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Context: The reported risk of hypothyroidism after hemithyroidectomy shows considerable heterogeneity in literature.

Objective: The aim of this systematic review and meta-analysis was to determine the overall risk of hypothyroidism, both clinical and subclinical, after hemithyroidectomy. Furthermore, we aimed to identify risk factors for postoperative hypothyroidism.

Data Sources: A systematic literature search was performed using several databases, including PubMed.

Study Selection: Original articles in which an incidence or prevalence of hypothyroidism after primary hemithyroidectomy could be extracted were included.

Data Extraction: Study identification and data extraction were performed independently by two reviewers. In case of disagreement, a third reviewer was consulted.

Data Synthesis: A total of 32 studies were included in this meta-analysis. Meta-analysis was performed using logistic regression with random effect at study level. The overall risk of hypothyroidism after hemithyroidectomy was 22% (95% confidence interval, 19–27). A clear distinction between clinical (supranormal TSH levels and subnormal thyroid hormone levels) and subclinical (supranormal TSH levels and thyroid hormone levels within the normal range) hypothyroidism was provided in four studies. These studies reported on an estimated risk of 12% for subclinical hypothyroidism and 4% for clinical hypothyroidism. Positive anti-thyroid peroxidase status is a relevant preoperative indicator of hypothyroidism after surgery. Effect estimates did not differ substantially between studies with lower risk of bias and studies with higher risk of bias.

Conclusions: This meta-analysis showed that approximately one in five patients will develop hypothyroidism after hemithyroidectomy, with clinical hypothyroidism in one of 25 operated patients. **(*J Clin Endocrinol Metab* 97: 2243–2255, 2012)**

Hemithyroidectomy is a frequently performed surgical operation. Indications for hemithyroidectomy include symptomatic unilateral goiter or toxic adenoma. Usually, its aim is to exclude malignancy in patients with solitary thyroid nodules with suspicious or indeterminate characteristics at fine-needle aspiration cytology (1). The majority of nodules are found to be histologically benign (1, 2). The price that is paid for the additional certainty provided by surgery is not negligible; postoperative bleeding, laryngeal nerve injury, wound infection, and hypothyroidism are well-known side effects of hemithyroidectomy (3). With the exception of postoperative hypothyroidism, most complications are rare.

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Abbreviations: CI, Confidence interval; fT3, free T_3; fT4, free T_4; TPO, thyroid peroxidase.

Hypothyroidism can be accompanied by a range of clinical manifestations, negatively impacting health status (3). Apart from the need for regular doctor visits and blood check-ups, long-term thyroid hormone therapy may be associated with accelerated loss of bone mineral density, atrial fibrillation, changes in left ventricular function, and impairment in psychological well-being (4–8). The reported risk of hypothyroidism after hemithyroidectomy varies greatly in the literature. This variation may be caused by different definitions of hypothyroidism, differences in patient characteristics between studied populations, follow-up duration, timing of thyroid hormone supplementation, and probably also surgical techniques.

The aim of the present meta-analysis was to determine the overall risk of hypothyroidism after hemithyroidectomy in preoperatively euthyroid patients, as well as the risk of clinically relevant hypothyroidism. Additionally, we intended to identify risk factors for the occurrence of hypothyroidism.

Materials and Methods

Eligibility criteria

Studies assessing thyroid function after hemithyroidectomy in euthyroid human populations of any age were eligible. No restrictions on publication date were imposed, but only regular articles or letters to the editor including full data were considered for inclusion. Meeting abstracts and unpublished results were not considered.

The intervention performed had to be a hemithyroidectomy with preservation of the contralateral lobe. Studies reporting on partial thyroidectomies were not included because that intervention can be more or less extended than hemithyroidectomy; including those studies could bias the estimated risk of hypothyroidism after hemithyroidectomy. The intervention could have been performed for several indications such as solitary nodule or multinodular goiter. We aimed to determine the risk of hypothyroidism after hemithyroidectomy in preoperatively euthyroid patients. Studies were verified for preoperative thyroid hormone status. Studies explicitly reporting on patients with hyperthyroidism before operation were excluded, unless only a minority of hyperthyroid patients was included (<15%) or when it was possible to extract data for the euthyroid subgroup. Studies not excluding patients with preoperative hypothyroidism or in which preoperative thyroid status was unknown were included; in a sensitivity analysis, studies with only preoperative euthyroid patients were analyzed. In case two publications reported data from the same cohort, the publication with the most complete data was included. Eligible studies were restricted to the English, Dutch, German, and French languages.

Endpoint definitions

The main outcome of the present meta-analysis was hypothyroidism. The definition of hypothyroidism was based on criteria used by authors of included studies. Whenever possible, a distinction was made between *subclinical hypothyroidism* [defined as free T_4 (fT_4), T_3, or free T_3 (fT_3) levels within the normal range with increased TSH levels] and *clinical hypothyroidism* (defined as fT_4, T_3, or fT_3 below the normal range as well as increased TSH levels) (9). Patients on postoperative thyroid hormone substitution were considered to have subclinical or clinical hypothyroidism, even when a clear definition of hypothyroidism was not provided by the authors. Whenever a study reported data for sequential measurements of thyroid function, the latest thyroid function assessment was used to extract the proportion of hypothyroidism.

Information sources and search strategy

The search strategy was composed in cooperation with a trained scientific librarian (J.W.S.). The following databases were searched up to August 17, 2011: PubMed, EMBASE (OVID-version), Web of Science, COCHRANE Library, CINAHL (EbscoHOST-version), Academic Search Premier (EbscoHOST-version), ScienceDirect, Springer Journal web site, Wiley Journal web site, LWW-Journals (OVID-version), HighWire Press, Informahealth Journal web site, and Google Scholar.

For two concepts (hemithyroidectomy and hypothyroidism/thyroid hormones), relevant keyword variations were used, not only variations in the controlled vocabularies of the various databases, but also free text word variations. This search strategy was optimized for all consulted databases. The process of citation tracking was used to screen the articles considered relevant for this meta-analysis for citing articles. Reference lists of studies eligible for inclusion were hand-searched and checked for additional relevant articles. In Fig. 1, the complete search strategy is shown.

Study selection and data collection process

All identified articles were screened independently for eligibility by two reviewers (H.V. and M.L.). Potentially relevant articles were read in full-text. Data extraction from included studies was performed using a predefined extraction sheet, which was updated after a pilot test on five randomly selected relevant studies. All data extractions were completed independently by two reviewers (H.V. and M.L.). Disagreement on the screening or data extraction process was resolved by consensus after consulting a third reviewer (O.M.D.). Three authors of original studies were contacted for additional information (3, 10, 11).

Risk of bias in individual studies

The following study characteristics were considered relevant for the assessment of risk of bias for the present meta-analysis: 1) selection of the exposed cohort. For all studies it was assessed whether consecutive patients (or a random sample of those) were included. 2) Loss to follow-up. For all studies the proportion of patients lost to follow-up was determined. 3) Ascertainment of exposure status at baseline. For all studies, information on preoperative thyroid state and preoperative thyroid hormone use was extracted. Higher proportions of included patients with preoperatively known hypothyroidism will falsely increase the postoperative risk estimate. These three items of the risk of bias assessment were used to determine potential sources of heterogeneity in meta-regression analysis.

Study endpoints and statistical analysis

The primary outcome of this meta-analysis was defined as the risk of hypothyroidism after hemithyroidectomy, calculated by the number of patients developing hypothyroidism

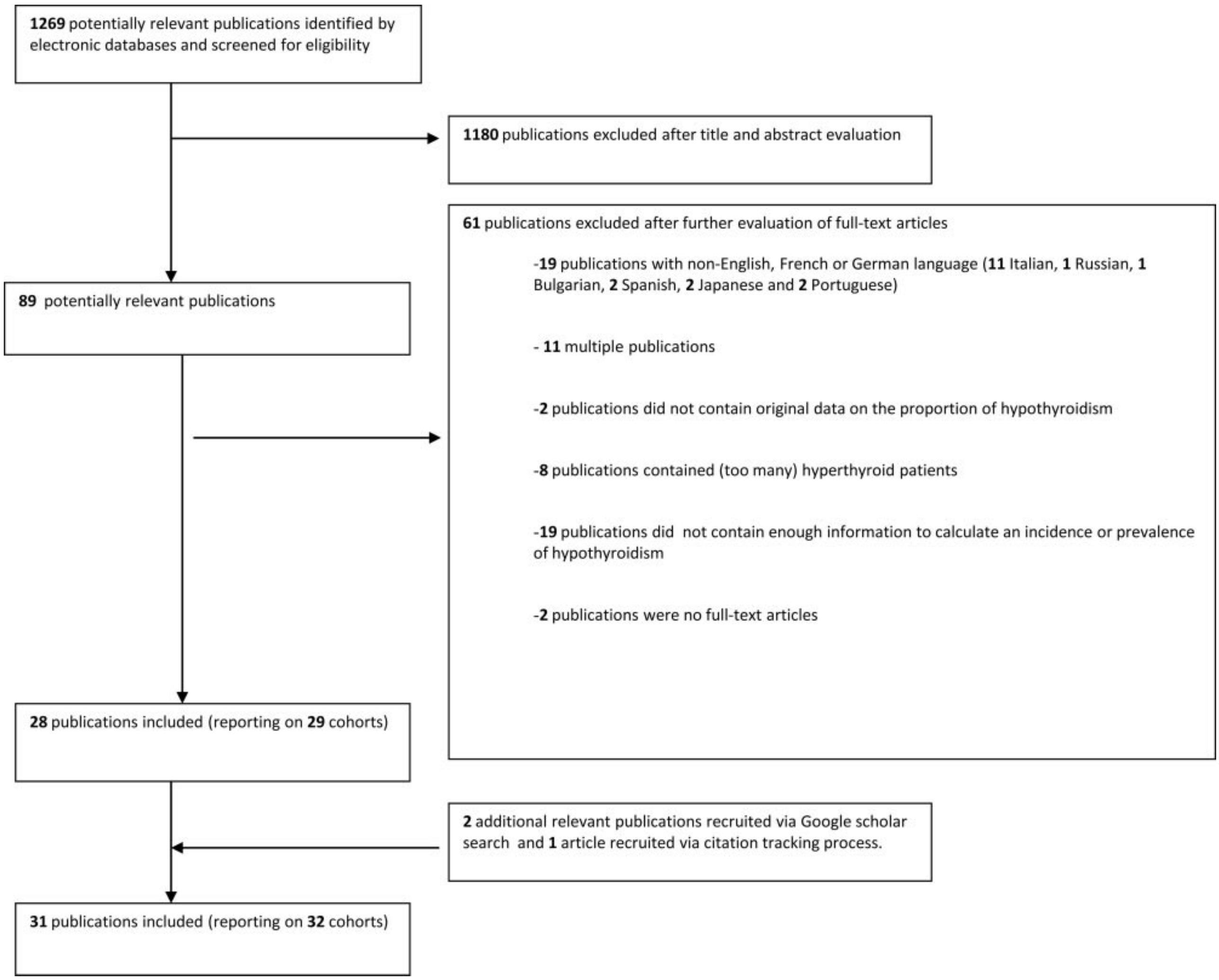

FIG. 1. Flow-chart.

after hemithyroidectomy divided by the total number of operated patients. For all proportions, exact confidence intervals (CI) were calculated. We aimed to calculate the *incidence* of hypothyroidism, defined as the proportion of preoperatively nonhypothyroid patients becoming hypothyroid after the procedure. If the authors did include preoperatively hypothyroid patients and did not provide data to calculate an incidence, the proportion of patients being hypothyroid postoperatively was defined as a *prevalence*. In case it was unclear whether patients had hypothyroidism before the operation, the reported proportion was regarded to be a prevalence. We calculated a weighted incidence and a weighted prevalence. Where possible, the pooled proportions where calculated separately for both clinical and subclinical hypothyroidism.

Meta-analysis was performed using an exact likelihood approach, more specifically logistic regression with random effect at the study level (12). Given the expected clinical heterogeneity, a random effects model was performed by default, and no fixed effects analyses were performed. For meta-analysis of proportions, the exact likelihood approach based on a binomial distribution has advantages compared with a standard random effects model that is based on a normal distribution (13). First, estimates from a binomial model are less biased than estimates from models based on a normal approximation (14). This is especially the case for proportions that are close to 0 or 1. Secondly, no assumptions are needed for the exact approximation when dealing with zero-cells, whereas the standard approach needs to add an arbitrary value (often 0.5) when dealing with zero-cells, contributing to a biased estimate of the model (15). Meta-regression analyses were also performed with an exact likelihood approach. All analyses were performed with STATA 12.0 (Stata Corp., College Station, TX).

Results

Study selection (Fig. 1)

The search of the electronic databases yielded a total of 1269 unique references that were evaluated by title and abstract. A total of 1180 references did not meet the eligibility criteria and were excluded. After reading the full manuscripts of the remaining 89 references in detail, 61 studies were excluded for the following reasons: language other than English, Dutch, German, or French (n = 19), data also reported in another included article (n = 11), no

TABLE 1. Characteristics of included studies

First author, year of publication (Ref.)	Indication for hemithyroidectomy	n	Female sex (%)	Mean age (yr)	Proportion of hypothyroidism after hemithyroidectomy, n (%)
Barczynski, 2010 (70)	Unilateral multinodular goiter	72	86.1	40.1	Incidence, 17/72 (23.6%)
Beisa, 2010 (46)	Variety of indications	216	89.8	44.1	Incidence, 48/216 (22.2%)
Berglund, 1991 (53)	Nontoxic goiter in most cases presenting clinically as a solitary cold nodule	177[h]	82.5	Median, 47.0	Prevalence, 13/177 (7.4%)
Berglund, 1998 (10)	Nontoxic benign goiter/unilateral thyroid nodule	26	76.9	Median, 48.5	Incidence, 0/26 (0%)
Buchanan, 2001 (56)	Solitary nodule or predominantly unilateral multinodular goiter	158	88.1[a]	46.5[a]	Incidence, 38/158 (24.1%)
Cheung, 1986 (51)	Removal of a solitary nodule	103	77.7	39.0	Incidence, 13/103 (12.6%)[d]
Chu, 2011 (74)	Unilateral thyroid mass that is either symptomatic or suspicious of malignancy	263	77.6	Median, 47.9	Incidence, 38/263 (14.4%)
De Carlucci, 2008 (64)	Surgery for nontoxic goiter	186	87.6	Median, 45.0	Incidence, 61/186 (32.8%)
Dobrinja, 2010 (48)	Solitary indeterminate follicular thyroid nodule	57	82.5	52.0	Prevalence, 23/57 (40.4%)
Farkas, 2002 (58)	Dominant thyroid nodule (enlarging/suspicious nodule, 118 cases; compression symptoms, 10 cases; cosmetic concerns, 3 cases)	131	88.5	45.5	Prevalence, 64/131 (48.9%)
Guberti, 2002 (57)	Benign nodular disease	35[e]; 63[f]	88.6[e]; 89.1[f]	71.0[e]; 40.0[f]	Prevalence, at least, 14/35 (40%)[e]; at least, 16/63 (25%)[f]
Hedman, 1986 (50)	Benign goiter	81[i]	83.2[a]	45.0[a]	Prevalence, 11/81 (13.6%)
Koh, 2008 (67)	Variety of indications	136	84.6	42.7	Incidence, 58/136 (42.6%)
Lankarani, 2008 (47)	Toxic multinodular goiter, nontoxic multinodular goiter, single nodule, Graves' disease	45	70.6[a]	39.0[a]	Incidence, 8/45 (17.8%)
Lee, 1989 (52)	Nontoxic solitary nodular goiter	18	95.5[a]	37.0[a]	Incidence, 1/18 (5.6%)
Lindblom, 2001 (55)	Solitary cold nodule in 33 cases, autonomous solitary nodule in 5 cases, and nontoxic goiter with compression in 7 cases	37[m]	86.7[a]	Median, 44.0[a]	Incidence, 8/37 (21.6%)
Lombardi, 1983 (49)	Euthyroid goiter/unilateral cold nodule	35	77.1	Range, 22–58 yr	Incidence, 2/35 (5.7%)
McHenry, 2000 (54)	FNA consistent with follicular/Hürthle cell neoplasm, 37 cases; progressive nodule growth +- compressive symptoms, 13 cases; persistently nondiagnostic FNA, 10 cases; exclusion of malignancy, 6 cases; incidental nodule, 4 cases; suppurative thyroiditis, 1 case	71	83.1	45.1	Incidence, 25/71 (35%)
Miller, 2006 (61)	Unclear	90	81.1	45.0	Incidence, 24/90 (27%)
Moon, 2008 (65)	Thyroid nodules	101	75.2	47.5	Incidence, 35/98 (35.7%); prevalence, 37/101 (36.6%)
Phitayakorn, 2009 (69)	Benign nodular thyroid disease (progressive increase in nodule size; substernal extension; development of compressive symptoms; radiographic evidence of tracheal, esophageal, or vessel impingement; cosmetic concerns; thyrotoxicosis)	260	83.5	48.0	Prevalence, 70/260 (26.9%)
Piper, 2005 (59)	Unclear	66	69.7	46.5	Incidence, 12/66 (18.2%)

(*Continued*)

TABLE 1. Continued

Definition of hypothyroidism	Preoperative TSH levels (mean ± SD)	Time to diagnosis since intervention	Thyroid function measurements after surgery
No definition provided	Not reported	Not reported	3, 6, 9, 12 months after surgery; every 12 months for the following years; up to 60 months with fT_3, fT_4 and TSH measurement
TSH >4.0 mIU/liter	0.79 ± 0.5 mIU/liter[b]; 1.42 ± 1.0 mIU/liter[c]	Majority detected within 2 months (77.1%)	2, 6, and 20 months after surgery TSH measurement
TSH >8 mIU/liter ± T_3 <0.9 nmol/liter ± clinical symptoms	Not reported	Manifest, one patient at 1 month and one patient at 6 months after surgery; latent, median 3 months (range, 1–48) after surgery	After surgery at 1, 3, 6, and 12 months, and once a year thereafter, with T_3 and TSH measurement
No definition provided	1.00 (range, 0.10–2.92) mIU/liter[b]	Not reported	After surgery at 1, 3, 6, and 12 months, T_4, T_3, and TSH were measured
TSH >3.5 mIU/liter ± fT_4 <10 pmol/liter	Not reported	All hypothyroid cases determined within 2 yr of follow-up	After surgery at 4 wk, 3 and 6 months, 1 and 2 yr with TSH and fT_4 measurement
T_4 <75 nmol/liter and/or TSH >7 mIU/ml	Not reported	Not reported	At 6 months, 1, 2, 3 yr after surgery T_4 and TSH measurement (1/3 of study population all occasions)
TSH >5.5 mIU/liter at any point during postoperative period	Median, 0.97 mIU/liter[b]; 1.75 mIU/liter[c]	Median, 3 months after surgery; majority [26/38 (68.4%)] developed within 6 months. All patients (n = 38) within 47 months	At 2 wk, 3 and 6 months, and afterward yearly serum TSH was monitored after surgery until the patient was lost to follow-up evaluation.
TSH >5.5 mIU/liter 4–8 wk after surgery	1.2 mIU/liter[b]; 2.1 mIU/liter[c]	4–8 wk after surgery	TSH measurement, 4–8 wk after surgery
No definition provided	Not reported	Not reported	In all patients, thyroid function testing (TSH, fT_4, thyroglobulin, TAA) 1 month after surgery
Biochemical, based on elevated TSH level; cutoff level not reported	Not reported	Not reported	TSH measurement, not reported which time period after surgery
No definition provided	Not reported	Not reported	TSH, fT_4 and fT_3 measurement, not reported which time period after surgery
TSH >8 mIU/liter ± fT_4 <9 pmol/liter or clinical symptoms	Not reported	Not reported	Thyroid function measurements (TSH, fT_4 and T_3), not reported which time period
TSH >4 mIU/liter ± fT_4 <0.7 ng/dl ± clinical symptoms	1.29 ± 0.90 mIU/liter[b]; 2.15 ± 1.30 mIU/liter[c]	Most hypothyroid cases (84.5%) were detected at 1 or 6 months after surgery	TSH and fT_4 measurements at 1, 6, and 12 months after surgery
No definition provided	Not reported	At least the incidence of hypothyroidism was determined within the first year after surgery	Thyroid function measurements (TSH, T_4 and T_3) + evaluation of clinical symptoms after surgery, monthly during the first 3 months, then 2-monthly, and then on a 3-month basis
Biochemical, TSH >6.5 mIU/liter	Not reported	6 wk after surgery	Thyroid function measurements (T_3, T_4, fT_4, rT_3, TSH) at first and second day after surgery and 6 wk after surgery
No definition provided	1.11 ± 0.48 mIU/liter[b]; 1.67 ± 0.98 mIU/liter[c]	Not reported	Thyroid function measurements (TSH, fT_4 and fT_3) at least 1 yr after surgery; unclear before this date
Biochemical, supranormal TSH levels (no reference range reported)	Not reported	24–30 months after surgery	Thyroid function measurements (T_3, fT_3, T_4, fT_4, TSH) at 12–18 months and 24–30 months after surgery
TSH >3.59 mIU/liter ± clinical symptoms	1.10 ± 0.74 mIU/liter[b]; 1.94 ± 1.00 mIU/liter[c]	In all but two patients, hypothyroidism was diagnosed within 8 wk after surgery; two other patients were diagnosed 6 and 7 yr later, due to inadequate follow-up in one	In all patients at least 5 wk after surgery, a TSH measurement
TSH >6.0 mIU/liter	1.95 ± 0.92 mIU/liter[b]; 3.15 ± 1.14 mIU/liter[c]	More than 75% hypothyroid cases developed within 9 months; mean, 6.6 months	In all patients 8 to 10 wk after surgery, TSH measurement; subsequently every 3–4 months, TSH measurement
TSH >4.7 mIU/liter	1.22 ± 0.89 mIU/liter[b]; 2.46 ± 1.16 mIU/liter[c]	More than 75% of hypothyroid cases within 9 months	At least 2 months after surgery TSH measurement; thereafter every 2–3 months, for 1 yr in all patients
Most likely biochemical, based on elevated TSH levels	Not reported	Not reported	Yearly TSH measurement
TSH >5.5 mIU/liter ± clinical symptoms	1.04 ± 0.70 mIU/liter[b]; 1.94 ± 1.20 mIU/liter[c]	Majority detected within 6 months	70% of patients initial TSH drawn first 3 months, 12% within 4–6 months, 12% within 7–12 months; 6% not in the first year

(*Continued*)

TABLE 1. Continued

First author, year of publication (Ref.)	Indication for hemithyroidectomy	n	Female sex (%)	Mean age (yr)	Proportion of hypothyroidism after hemithyroidectomy, n (%)
Rosario, 2006 (60)	Indeterminate solitary nodule	85	68.1[a]	Median, 49.0[a]	Prevalence, 27/85 (31.8%)
Seiberling, 2007 (62)	Benign nontoxic thyroid disease	58	75.9	46.5	Incidence, 14/58 (24.1%)
Spanheimer, 2011 (72)	Nodular thyroid disease	65[l]	83.2[a]	50.1[a]	Incidence, 24/65 (36.9%)
Stoll, 2009 (3)	Lobectomy for various indications including, goiter, follicular neoplasm	547	80.4	50.0	Incidence, 78/547 (14.3%)
Su, 2009 (68)	Malignant FNA, 1 case; recurrent cyst, 10 cases; solitary nodule, 145 cases; multinodular goiter, 138 cases	247[g]	85.7[a]	50.0[a]	Incidence, 27/247 (10.9%)[g]
Tomoda, 2011 (73)	Indeterminate thyroid nodules	233	82.8	51.0	Incidence, 57/233 (24.4%)
Vaiman, 2008 (66)	Multinodular goiter[k]	1051	58.2[a,k]	46.8[a,k]	Prevalence, 294/1051 (28.0%)
Wormald, 2008 (63)	Exclusion of malignancy and relief of compressive symptoms for unilateral thyroid mass	82	86.6	53.0	Incidence, 15/82 (18.3%)
Yetkin, 2010 (71)	Nontoxic benign nodular goiter	104	88.5	44.9	Prevalence, 24/104 (23.1%)

FNA, Fine-needle aspiration; T_3, total T_3; T_4, total T_4; TAA, thyroid autoantibodies.

[a] Determined in a larger population, used as a surrogate for the actual hemithyroidectomized population included in this meta-analysis.

[b] Determined within patient cohort euthyroid after hemithyroidectomy.

[c] Determined within patient cohort hypothyroid after hemithyroidectomy.

[d] Cheung *et al.*: 71 patients had both T_4 and TSH determined, 17 had T_4 only, and 15 had TSH only (71 + 17 + 15 = 103).

[e] Guberti *et al.*: determined in old group of patients with mean age of 71 yr.

[f] Guberti *et al.*: determined in young group of patients with mean age of 40 yr.

[g] Su *et al.*: determined in a euthyroid population with preoperative TSH levels in the normal range (0.5–4.0 mIU/liter), excluding 47 patients with subnormal TSH levels (<0.5 mIU/liter) before surgery.

[h] Berglund *et al.*: total patient cohort consisted of 177 patients, with a maximum of 20 patients who underwent partial unilateral thyroid resection instead of a hemithyroidectomy.

[i] Hedman *et al.*: 81 of 92 patients could be analyzed because 37 were not on thyroid hormone after the hemithyroidectomy and 44 patients agreed to stop treatment for at least 6 wk to evaluate thyroid function; 27 of the 81 patients (33.3%) had a small remnant left on the lobectomized side.

[k] Vaiman *et al.*: based on total population of 3470 patients who underwent partial thyroidectomy [subtotal thyroidectomy, near-total thyroidectomy, and hemithyroidectomy (n = 1051)].

[l] Spannheimer *et al.*: six patients on postoperative thyroid hormone for nodule suppression in the contralateral thyroid lobe were excluded from analysis.

[m] Lindblom *et al.*: determined in a euthyroid population with preoperative TSH levels in the normal range; eight patients with preoperative subclinical hyperthyroidism were excluded from analysis.

original data on the proportion of hypothyroidism after hemithyroidectomy (n = 2) (16, 17), cohort including a substantial number (>15%) of hyperthyroid patients (n = 8) (18–25), inability to calculate a prevalence or incidence from the data provided (n = 19) (11, 26–43), and no regular article (n = 2) (44, 45). Google Scholar search provided two more relevant articles to include in this meta-analysis (46, 47), and one additional article was included after citation tracking of included articles (48). Finally, 31 publications were included in the present meta-analysis (3, 10, 46–74). These 31 publications reported on 32 cohorts.

Study characteristics

Study characteristics are summarized in Table 1. A total of 4899 patients were included in this meta-analysis. The largest study comprised 1051 patients (66). Years of pub-

TABLE 1. Continued

Definition of hypothyroidism	Preoperative TSH levels (mean ± SD)	Time to diagnosis since intervention	Thyroid function measurements after surgery
TSH >10 mIU/ml single measurement or 5–10 mIU/ml two consecutive measurements (interval, 6–8 wk)	Not reported	Majority (66%) diagnosed in the first year of follow-up	After surgery at 6 months interval TSH measurement
TSH >4.0 mIU/ml ± subnormal fT_4 ± clinical symptoms	1.07 (95% CI, 1.01–1.37) mIU/liter[b]; 2.39 (95% CI, 1.53–2.94) mIU/liter[c]	All but one of the 14 hypothyroid patients had been diagnosed so within 2 months	At least one TSH measurement drawn within 6 wk after surgery in all patients; furthermore, measurements were variable in all patients
TSH >4.20 mIU/ml	Not reported	6 wk after surgery	TSH measurement at 6 wk after surgery
TSH >4.82 mIU/ml measured at least 6 wk after surgery	1.35 ± 0.07 mIU/ml[b]; 2.12 ± 0.26 mIU/ml[c]	6–8 wk after surgery	TSH measurement 6–8 wk after surgery
TSH >4.0 mIU/liter	All 247 patients had preoperative TSH levels of 0.5–4.0 mIU/liter	68% of hypothyroid cases were diagnosed by 6 months, 90% by 15 months	Not reported
TSH >5.0 mIU/liter + normal fT_4 lasting >3 months after surgery	1.24 ± 0.82 mIU/liter[b]; 2.73 ± 1.36 mIU/liter[c]	More than 90% hypothyroid cases within 6 months; 56/233 needed T_4 after surgery at 12 months	TSH measurement at least 4–6 wk after surgery; subsequently every 3–6 months for at least 3 yr
Serum TSH >6.0 mIU/liter at 6 months and more after surgery	Not reported	Not reported	Not reported
TSH >4.5 mIU/liter ± subnormal fT_4 ± clinical symptoms	Not reported	Clinical, 5.4 months (range, 3–6); subclinical, 12 months (6–12)	TSH measurement once between 3 and 6 months after surgery, at 12 months, thereafter annually; T_4 measurement not reported
TSH >5 mIU/liter	Not reported	Not reported	Thyroid function measurements (fT_4 and TSH) in all patients at the end of the first months after surgery; afterward, every 6 wk

lication ranged from 1983 to 2011. Mean age of the study populations ranged from 37 to 71 yr. In all studies, the majority of patients were female, with proportions ranging from 58–96%. In one manuscript, the risk of hypothyroidism was reported separately for two study populations: a younger cohort (mean age, 40 yr) and an older cohort (mean age, 71 yr) (57).

Hemithyroidectomies were performed for various indications, such as indeterminate thyroid nodules, nodules causing symptoms, follicular neoplasm, and nontoxic goiter.

Hypothyroidism was defined as an increased TSH level with or without subnormal thyroid hormone levels in 24 studies (75%). The eight remaining studies all measured TSH with additional thyroid function tests during follow-up but did not provide a formal definition of hypothyroidism in the manuscript. However, it is plausible that diagnosis in these eight studies also was

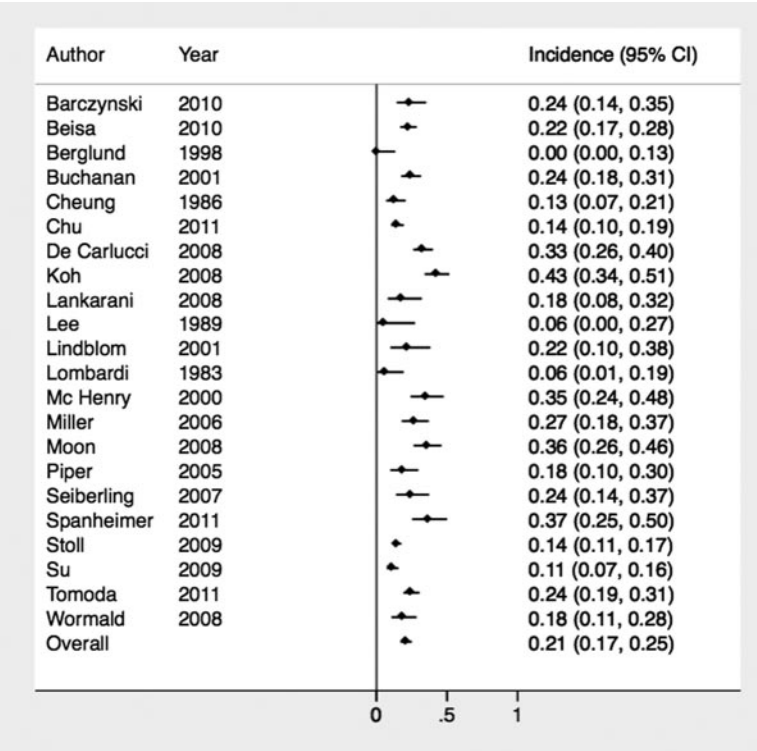

FIG. 2. Meta-analysis of the incidence of hypothyroidism after hemithyroidectomy.

based on biochemical testing of thyroid function. Different assays and cutoff levels were used. The number and timing of laboratory measurements varied from only one TSH measurement 4–8 wk after surgery to monthly, 2-monthly, or 3-monthly regular thyroid hormone measurements for years after the intervention. Postoperative TSH values are shown in Supplemental Table 1 (published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org).

Risk of bias assessment

Twenty-four studies reported to have included consecutive patients (3, 10, 46, 47, 53–56, 58–65, 67–74), whereas in three studies selected patients were included (48, 50, 66). In the remaining five studies, the selection procedure was not clearly reported (49, 51, 52, 57). Nineteen studies reported no loss to follow-up, and in one study loss to follow-up was negligible (10); one study reported 30% loss to follow-up after 12 months (74), and 11 studies did not report on loss to follow-up.

In 16 studies, only preoperatively euthyroid patients were included. In two studies, it was possible to extract data for preoperatively euthyroid patients (55, 68). In 13 studies, it was unclear whether all patients were euthyroid before surgery. One study included 10% preoperatively hyperthyroid patients (3). In one study, 18% of patients were on thyroid hormone therapy preoperatively (58). This study was included, with the proportion of hypothyroidism after the intervention regarded a prevalence. See Supplemental Table 2 for more details.

Meta-analysis and meta-regression (Figs. 2 and 3)

The pooled risk of hypothyroidism after hemithyroidectomy was 22% (95% CI, 19–27). In 22 studies, the incidence of hypothyroidism after hemithyroidectomy could be calculated.

The reported incidences ranged from 0 to 43%. The weighted pooled incidence of hypothyroidism after hemithyroidectomy was 21% (95% CI, 17–25). A similar incidence of 22% (95% CI, 18–27) was found when restricting the analysis to studies with inclusion of preoperative euthyroid patients only. From 11 studies, the prevalence could be calculated. Reported prevalences ranged from 7 to 49%. The weighted pooled prevalence of hypothyroidism after hemithyroidectomy was 27% (95% CI, 20–36).

In a random-effects meta-regression, inclusion of consecutive patients ($P = 0.90$) or the explicit absence of loss to follow-up ($P = 0.93$) was not associated with the risk of hypothyroidism. Also, the inclusion of only euthyroid patients did not affect the risk of hypothyroidism ($P = 0.78$).

A clear biochemical distinction between clinical and subclinical hypothyroidism was reported in four studies only (50, 53, 63, 67). Based on these four studies (n = 476 patients), the overall risk was 12% (95% CI, 5–25) for subclinical hypothyroidism and 4% (95% CI, 2–8) for clinical hypothyroidism. In studies clearly reporting time to diagnosis since intervention, it was shown that hypothyroidism was usually detected within the first 6 months after hemithyroidectomy (46, 53, 54, 59, 61–63, 67, 68, 73, 74). Albeit, later occurrences of hypothyroidism were possible (74).

Analysis of risk factors for hypothyroidism after hemithyroidectomy

Although older age was reported to be a significant risk factor in four studies (46, 55, 73, 74), these findings could not be replicated in eight other studies (3, 54, 61, 62, 64, 65, 67, 68). Higher preoperative TSH level was a significant risk factor for hypothyroidism after hemithyroidectomy in 13 studies (3, 46, 54, 60–65, 67, 68, 73, 74). In 12 of these studies (92%), this assessment was based on preoperative euthyroid patients, meaning that higher TSH levels within the normal range are a risk factor.

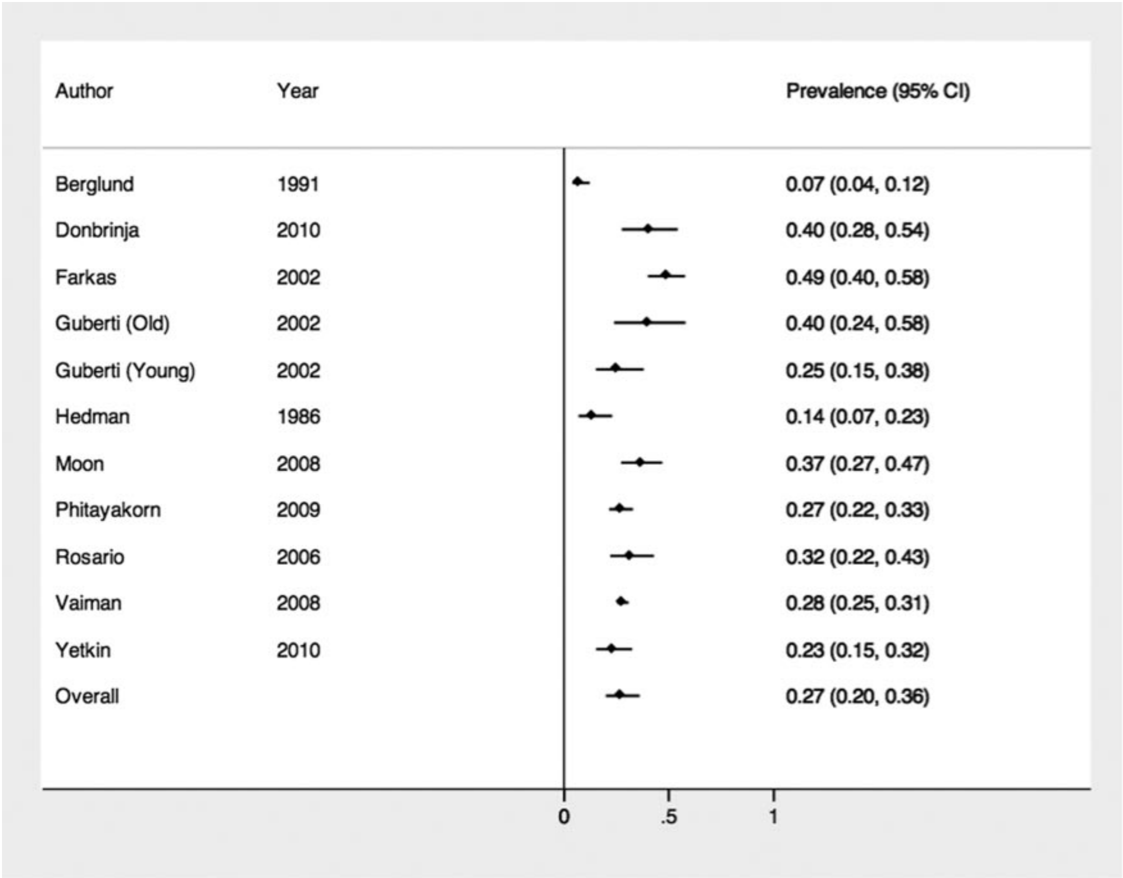

FIG. 3. Meta-analysis of the prevalence of hypothyroidism after hemithyroidectomy.

An increased risk for hypothyroidism in patients with anti-thyroid peroxidase (anti-TPO) antibody positivity was consistently reported in six studies (56, 60, 64, 67, 68, 74). The impact of anti-thyroglobulin antibodies showed conflicting results (64, 67, 73, 74). Concomitant thyroiditis was assessed in 13 studies and was considered a significant risk factor for hypothyroidism in 11 studies (3, 53, 56, 59, 61–63, 67, 68, 72, 74). See Supplemental Table 3 for more detailed information.

For two determinants, anti-TPO status and lymphocytic infiltration in the resected lobe, data were provided in sufficient detail to perform a quantitative analysis. In six studies, comprising 791 patients, the risk of hypothyroidism in patients with anti-TPO antibodies was compared with the risk in patients without these antibodies. The risk for hypothyroidism was clearly higher (48%; 95% CI, 41–54) in patients with positive anti-TPO antibodies than in patients without antibodies (19%; 95% CI, 13–27; $P = 0.001$).

Similarly, we calculated the risk for hypothyroidism in patients with no inflammation or a low degree (grade 0–2) compared with patients with a high degree of inflammation (grade 3–4) in the resected lobe. In four studies, comprising 459 patients, a quantitative analysis was based on the same scoring system for lymphocytic infiltration (53). These four studies were used in formal meta-analysis. The risk for hypothyroidism was higher (49%; 95% CI, 34–63) in patients with a high degree of inflammation than in patients with no inflammation or a low degree (10%; 95% CI, 3–26; $P = 0.006$). Due to major differences in the definition of thyroiditis, we did not use thyroiditis as a formal demarcation criterion for further quantitative analysis.

Discussion

The present meta-analysis showed that the overall risk of hypothyroidism after hemithyroidectomy was 22%. When restricting the analysis to studies reporting a true incidence, the risk for hypothyroidism was 21%, a large proportion of those having subclinical hypothyroidism.

There are some limitations that should be taken into account when interpreting this meta-analysis. First, the available data did not allow us to assess what proportion of the reported hypothyroidism is transient or permanent. Once thyroid hormone replacement is started, spontaneous recovery of thyroid function could be missed. Furthermore, timing of thyroid function measurement showed variation ranging from only one assessment relatively soon after the intervention to regular follow-up measurements during several years. Measuring thyroid function relatively early after the procedure without follow-up may increase the likelihood of only detecting a transient compensating TSH elevation and not a true state of hypothyroidism. Unfortunately, only a few studies have clearly investigated this issue (11, 46, 49, 51). A main obstacle in determining to which extent hypothyroidism is only a transient phenomenon is that the majority of studies do not report the time course of TSH levels in patients who develop hypothyroidism. Frequently, when hypothyroidism occurred, patients received thyroid hormone substitution, masking whether hypothyroidism would have recovered naturally. One study reported that in untreated hypothyroid patients, TSH levels progressively decreased during the first 20 months after surgery (46). Another study reported that in 33% of patients with hypothyroidism, TSH levels normalized within 28 months after the intervention (59). A recent study showed a risk of 17% for early postoperative hypothyroidism and 8% for persistent hypothyroidism, showing that hypothyroidism can be a transient phenomenon at least in some patients (11). However, these results should be interpreted carefully because patients in whom a near-total lobectomy was pursued were also studied, which is the reason for not including this study in our meta-analysis. Normalization of thyroid function after a thyroid lobectomy may take a relatively long time period (49, 51, 59).

Authors defined hypothyroidism differently, although the use of biochemical parameters (TSH levels above the upper limit of normal) was a common means of determining hypothyroid state in the vast majority of studies. In our meta-analysis, most of the detected thyroid dysfunction after hemithyroidectomy was subclinical hypothyroidism, although only four of the studies reported clear data on the distinction between subclinical and clinical hypothyroidism. Although subclinical hypothyroidism could have beneficial effects in the elderly (75), most patients undergoing hemithyroidectomy are under the age of 65 yr, and potential adverse consequences of subclinical hypothyroidism in middle-aged populations have been shown (9, 76–78). Furthermore, patients with subclinical hypothyroidism are at increased risk of developing clinical hypothyroidism (79). Because patients with subclinical hypothyroidism due to a hemithyroidectomy differ from patients with "spontaneous" subclinical hypothyroidism, it is difficult to extrapolate the risks derived from studies including hypothyroid patients to operated patient populations. The exact clinical implications of subclinical hypothyroidism in hemithyroidectomized populations have yet to be disentangled, and future trial studies should clarify the issue of whether treatment of subclinical hypothyroidism in this setting will be beneficial.

What factors will influence the risk of hypothyroidism after hemithyroidectomy? The technical performance of the procedure of hemithyroidectomy is quite straightforward and is supposed to include resection of the isthmus. However, we cannot exclude that small variations in the extent of the resection may exist and may impact the risk of hypothyroidism because smaller remnant thyroid volume has been shown to increase the risk of postoperative hypothyroidism (64, 65). Our analysis showed that concomitant thyroiditis in the excised thyroid lobe, TSH levels in the higher-normal range, and positive anti-TPO antibody levels are risk factors for the development of hypothyroidism. As our quantitative analysis implied, anti-TPO-positive patients had considerably higher risk (almost 50%) of hypothyroidism in comparison to anti-TPO-negative patients. In the individual patient, preoperative anti-TPO measurement may be used as a simple tool to estimate the risk of hypothyroidism in more detail before planning surgery. Factors such as older age, positive thyroglobulin autoantibody levels, laterality of the resected lobe, and weight of the resected thyroid tissue were not consistently reported to be risk factors. In this meta-analysis, studies were performed in countries in which iodine status may vary. Because moderate to severe iodine deficiency increases the risk of hypothyroidism (80), iodine-deficient patients undergoing hemithyroidectomy may be more prone to develop hypothyroidism than iodine-sufficient patients. Of the studies included in this meta-analysis, the study of Yetkin *et al.* (71), performed in Turkey, comprised a population with potential iodine-deficient patients according to a World Health Organization publication with data on iodine status by country (81). This study showed a risk for postoperative hypothyroidism (23%) similar to the overall pooled risk from our meta-analysis.

The American Thyroid Association Guidelines for the treatment of thyroid nodules recommend total thyroid lobectomy for isolated indeterminate solitary thyroid nodule for those who prefer a more limited surgical procedure (1). Although most advantages and disadvantages of the performance of hemithyroidectomy can be disentangled before surgery, the risk of hypothyroidism after hemithyroidectomy is an important element in decision-making for the individual patient, the health care provider, as well as the policy makers.

In conclusion, this meta-analysis showed that approximately one in five patients will develop some form of hypothyroidism after thyroid lobectomy, with clinical hypothyroidism in one of 25 operated patients. TSH level in the higher-normal range and positive anti-TPO status are significant preoperative indicators of thyroid failure after surgery. More studies are required to assess in what proportion hypothyroidism after thyroid lobectomy is a transient phenomenon.

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