

BMJ Open Birth control pills and risk of hypothyroidism: a cross-sectional study of the National Health and Nutrition Examination Survey, 2007–2012

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ABSTRACT

Objective The association between use of birth control pills and thyroid function in women has not ever been well studied, but potential risk has been implicated by small sample-sized studies. We aimed to determine this association using a large epidemiological survey.

Design Cross-sectional study.

Setting National Health and Nutrition Examination Survey conducted in the USA from 2007 to 2012.

Participants Female respondents aged 18+ who had data on history of taking birth control pills and thyroid function were included. History of taking birth control pills was based on responses on the reproductive health questionnaire. Participants not on antithyroid medication with thyroid-stimulating hormone (TSH) >5.6 mIU/L and those on thyroid hormone replacement regardless of TSH were categorised as hypothyroid. Participants not on thyroid hormone replacement or antithyroid medication who had TSH between 0.34 mIU/L and 5.6 mIU/L were classified as euthyroid.

Primary and secondary outcome measures Association between use of birth control pills and hypothyroidism based on multivariate logistic regression analysis.

Results A total of 5116 female adults with history of taking birth control pills (n=3034) and without (n=2082) were included. A higher prevalence of hypothyroidism was found in those who have ever taken birth control pills (17.7% vs 14.1%; p=0.003). Multivariate logistic regression adjusted for confounding covariables, including age, race, education, body mass index, smoking status, alcohol use, history of thyroid disease, current thyroid disease, first menstrual age, pregnancy history, menopause status and history of hormone replacement use, demonstrated a significant association between history of taking birth control pills for more than 10 years and hypothyroidism (OR, 3.837; 95% CI 1.402 to 10.500; p=0.009).

Conclusions Longer history of using birth control pills was strongly associated with hypothyroidism, especially for more than 10 years.

INTRODUCTION

Birth control pills have developed quickly and have been widely used by an increasing number of women of childbearing potential

Strengths and limitations of this study

- This study benefited from the large, nationally representative data set and rigorous research methods of the National Health and Nutrition Examination Survey.
- The study explored the association between oral contraception and hypothyroidism for the first time and controlled for important confounders.
- The limitations of this study were that data were derived from cross-sectional studies and that the relationship was not necessarily identified as causal.
- Use of self-reported data might result in recall bias.

since their introduction.¹ As the most common form of effective and reversible contraception, the prevalence of use of birth control pills among women aged 15–45 is 17% and 27.3% among all methods of contraception in the USA. Moreover, use of birth control pills declined as age increased: 54% of users of contraceptives were under 20 years old, 35% were 20–40 years old, and only 11% were 40–45 years old.² Youth and popularisation of birth control pills warrant further research and investigation with regard to safety, especially long-term safety. Birth control pills were first designed to inhibit ovulation and are thus used for birth control.³ Over time, they did not only help prevent unwanted pregnancies but are also used as treatment for abnormal uterine bleeding, endometriosis, menstrual and hormonal disorder, etc. Additionally, long-term use of birth control pills (≥10 years) could significantly decrease the risk of ovarian and endometrial cancer.⁴ However, they could also bring many adverse effects, including increased risk of hypertension, thromboembolic events, breast cancer, serious autoimmune diseases, and especially endocrine-related dysfunctions.^{5,6}

Thyroid hormone, one of the most notable endocrine hormones, is crucial for normal growth, energy metabolism and reproduction. Hypothyroidism is the most common pathological hormone insufficiency, and without treatment may be associated with a high risk of morbidity and mortality.⁷ It lacks specific symptoms at the early stage, but can lead to systemic symptoms such as chills and fatigue as the disease progresses, and eventually presents as myxoedema or even heart failure. The prevalence of hypothyroidism in the USA is 4.6% according to the National Health and Nutrition Examination Survey (NHANES) III study. The prevalence is approximately three to seven times higher in women compared with men and its incidence increases with age.^{7,8} Several drugs could cause hypothyroidism, the most notable being lithium, amiodarone and tyrosine kinase inhibitors.⁸ However, considering its higher incidence in women, there may be an association between medications commonly used by women and thyroid function. A literature review summarised two studies and reported that use of birth control pills was associated with a potentially higher risk of hypothyroidism.⁹ Strieder *et al*¹⁰ reported ever use of contraceptives was possibly associated with hypothyroidism (relative risk [RR], 4.232; 95% confidence interval [CI], 0.552 to 32.425) in a case-control study enrolling 29 cases. Similar trend was confirmed by Frank and Kay¹⁰ in their cohort study of 47 cases, showing an RR of 1.17 but a p value of 0.552.

In other words, the relationship between use of birth control pills and hypothyroidism has been observed, but existing studies were limited by their sample size and follow-up duration. We examined the NHANES database, which is representative of the US population, to determine whether use of birth control pills was associated with a higher risk of hypothyroidism.

MATERIALS AND METHODS

Patient and public involvement

We conducted a retrospective analysis of a cohort of US population of the NHANES, a periodic survey performed by National Center for Health Statistics. Informed consent has been obtained from every participant and therefore there was no need for any ethical consent in this study. The NHANES includes extensive demographic data, physical examinations, laboratory tests, health-related questionnaires and lists of prescription medications. NHANES 2007–2012 is the only continuous survey that collects data on reproductive health and thyroid function laboratory tests among US women. We included women who had information about taking birth control pills in the reproductive health questionnaire, reported thyroid medication use and had thyroid function laboratory test values. In the reproductive health questionnaire, the main questions were ‘Have you ever taken birth control pills?’ and ‘How long have you been taking birth control pills?’, with the choices ‘yes; no; refused or don’t know’, along with the exact number of years, respectively.

Knowledge of generic drug names was obtained from the prescription medications questionnaire, and the incidence of use of levothyroxine, methimazole and propylthiouracil was recorded. Thyroid-stimulating hormone (TSH) levels were determined through available data from thyroid profile tests using third-generation, two-site immunoenzymatic (‘sandwich’) assay (details in online supplemental file).

Definitions of thyroid condition

Thyroid condition was determined through patient report of currently taking medications and TSH tests in a manner similar to that of Thavaraputta *et al*,^{11,12} who reported the prevalence of thyroid disease in the USA using diagnostic criteria. NHANES documentation provides a reference range of 0.34–5.6 mIU/L for normal TSH based on manufacturer guidelines. Participants were determined to be hyperthyroid if they reported currently taking methimazole or propylthiouracil, regardless of TSH level, or if their TSH level was <0.34 mIU/L. If the remaining participants reported currently taking levothyroxine regardless of TSH level, or if their TSH level was >5.6 mIU/L, they were determined to be hypothyroid. Participants were determined to be euthyroid if they were included neither in the hyperthyroid nor hypothyroid group.

Covariables and grouping

Demographic information on age, race/ethnicity and education was recorded at the time of the interview. Body mass index (BMI) was coded into four categories based on standard cut-offs: underweight (<18.5 kg/m²), normal BMI (from 18.5 to <25 kg/m²), overweight (from 25 to <30 kg/m²) and obese (≥30 kg/m²). Smoking was coded into current, former or never, while alcohol use was coded into four categories from never up to three or more drinks per day. History and current knowledge of thyroid disease were also included.

Participants were divided into two groups according to whether they have ever taken birth control pills or not, as indicated on the reproductive health questionnaire. Participants with history of taking birth control pills were assigned to the history group; otherwise, they were assigned to no history group. Reproductive variables such as first menstrual age, pregnancy history, menopause status and history of hormone replacement use were included.

Missing covariables

The address of 11% of the participants could not be geocoded, which contributed to missing data in the cross-sectional analysis. As such, 10 multiple imputations using fully conditional specification were used to address potential biases arising from item non-response.

Statistical analysis

Statistical analyses were performed in StataSE V.14.2. χ^2 tests were used in the descriptive tables on population characteristics; multivariate logistic regression was used

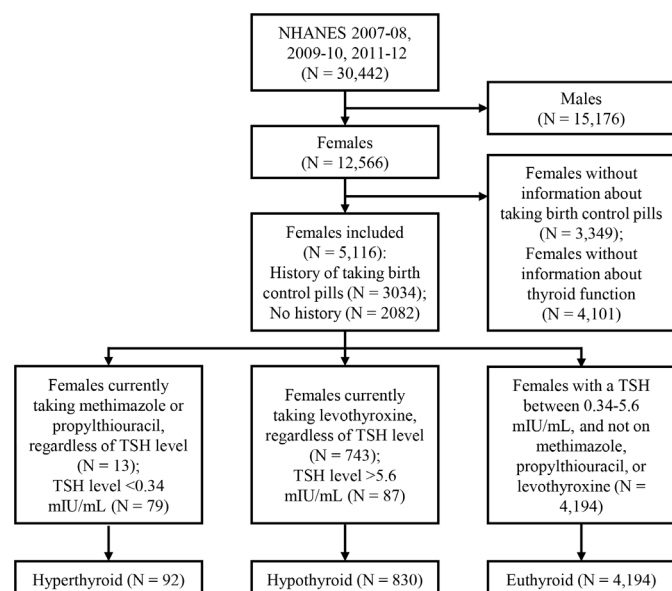


Figure 1 Schematic representation of participant selection and distribution of participant groups. NHANES, National Health and Nutrition Examination Survey; TSH, thyroid-stimulating hormone.

to estimate the odds of a hypothyroid diagnosis among participants with history of taking birth control pills. Coefficients of logistic regression models presented include an unadjusted model; followed by model 1, adjusting for demographic covariables including age, race and education; model 2, adjusting for all covariates in model 1, with individual covariables including BMI, smoking status, alcohol use, history of thyroid disease and current thyroid disease; and model 3, adjusting for all covariates in model 2, with gynaecological covariables including first menstrual age, pregnancy history, menopause status and history of hormone replacement use. History of taking birth control pills was subgrouped into history of <1 month, 1 month–1 year, 1–2 years, 2–10 years and >10 years. Statistical significance was set at $p < 0.05$.

Patient and public involvement

Patients and the public were not involved in the design of this study.

RESULTS

Population characteristics

The total number of participants in the 2007–2012 NHANES was 30 442. Only 5116 female subjects met the inclusion criteria, including 2082 and 3034 women who never took and were ever taking birth control pills, respectively (figure 1). Among the 3034 women who reported history of taking birth control pills, 210 (6.9%) have taken birth control pills for less than 1 month, 864 (28.5%) have a history of 1 month–1 year, 329 (10.8%) of 1–2 years, 1235 (40.7%) of 2–10 years, and 376 (12.4%) of longer than 10 years. Table 1 lists the demographic and health characteristics of the history group and no history group. Younger women (<65 years), non-Hispanic white

women, participants with higher education, obese participants, currently smoking, higher alcohol consumption, history of pregnancy or current pregnancy, and participants with later first menstrual age were of higher proportions of history of taking birth control pills than their counterparts. Menopause status, age of last menstruation and use of hormone replacement medications including oestrogen and progestin (not including birth control pills) were not different between the two groups. Among the 5116 participants, 830 were identified as hypothyroid, 4194 as euthyroid and 92 as hyperthyroid. Participants in the history group more frequently developed a hypothyroid status (17.7% vs 14.1%; $p = 0.003$), with no difference in history or current knowledge of thyroid disease.

Association between history of taking birth control pills and hypothyroidism

According to univariate analysis, participants with any history of taking birth control pills carried an OR of 1.280 (95% CI of 1.104 to 1.484) of developing hypothyroidism ($p = 0.001$). Participants with history of 2–10 years (OR, 1.329; 95% CI 1.108 to 1.595; $p = 0.002$) and >10 years (OR, 1.865; 95% CI 1.440 to 2.415; $p = 0.000$) were more likely to have a hypothyroidism diagnosis. After adjusting for model 1 (demographic covariables including age, race and education), participants with any history of taking birth control pills remained at high risk of developing hypothyroidism (OR, 1.245; 95% CI 1.043 to 1.486; $p = 0.015$). Participants with history of 1 month–1 year (OR, 1.293; 95% CI 1.021 to 1.636; $p = 0.033$), 2–10 years (OR, 1.262; 95% CI 1.022 to 1.559; $p = 0.030$) and >10 years (OR, 1.555; 95% CI 1.167 to 2.072; $p = 0.003$) were at higher risk of developing hypothyroidism. However, after adjusting for model 2, adding individual covariables including BMI, smoking status, alcohol use, history of thyroid disease and current thyroid disease, women with history of taking birth control pills for more than 10 years were at a higher risk of developing hypothyroidism (OR, 4.025; 95% CI 1.489 to 10.879; $p = 0.006$). Similarly, after adjusting for model 3, adding gynaecological covariables including first menstrual age, pregnancy history, menopause status, history of hormone replacement use and all variables in model 2, women with history of taking birth control pills for more than 10 years were at a higher risk of developing hypothyroidism (OR, 3.837; 95% CI 1.402 to 10.500; $p = 0.009$). All details are displayed in table 2. The association between history of taking birth control pills and hypothyroidism after excluding pregnant participants is shown in table 3. Similarly, after adjusting for model 3, history of taking birth control pills for more than 10 years was still associated with a higher risk of hypothyroidism (OR, 4.717; 95% CI 1.721 to 12.926; $p = 0.003$).

DISCUSSION

To the best of our knowledge, this is the first study to reveal a strong association between long-term use of birth control pills and hypothyroidism. Based on a large

Table 1 Demographic and clinical characteristics of the study population (N=5116)

| Variable | No history n (weighted %) | With history n (weighted %) | χ^2 | P value |
|--|------------------------------|--------------------------------|----------|---------|
| Age | | | | |
| ≤44 | 1050 (50.4) | 1396 (46.0) | 322.363 | <0.001 |
| 45–64 | 364 (17.5) | 1153 (38.0) | | |
| ≥65 | 668 (32.1) | 485 (16.0) | | |
| Race | | | | |
| Mexican American | 412 (19.8) | 465 (15.3) | 87.855 | <0.001 |
| Other Hispanic | 280 (13.4) | 334 (11.0) | | |
| Non-Hispanic white | 792 (38.0) | 1487 (49.0) | | |
| Non-Hispanic black | 417 (20.0) | 610 (20.1) | | |
| Other race | 181 (8.7) | 138 (4.5) | | |
| Education | | | | |
| Less than high school diploma | 540 (37.5) | 664 (22.9) | 135.868 | <0.001 |
| High school diploma | 347 (24.1) | 622 (21.4) | | |
| Some college | 337 (23.4) | 955 (32.9) | | |
| College or more | 215 (14.9) | 661 (22.8) | | |
| Body mass index status | | | | |
| Underweight | 90 (4.4) | 64 (2.1) | 67.598 | <0.001 |
| Normal | 735 (35.9) | 864 (28.8) | | |
| Overweight | 581 (28.4) | 865 (28.8) | | |
| Obese | 640 (31.3) | 1212 (40.3) | | |
| Smoking status | | | | |
| Never | 989 (68.5) | 1707 (58.8) | 44.868 | <0.001 |
| Former | 265 (18.4) | 611 (21.1) | | |
| Current | 189 (13.1) | 584 (20.1) | | |
| Alcohol use | | | | |
| Never or not in the last 12 months | 809 (61.9) | 970 (36.7) | 239.567 | <0.001 |
| 1 drink/day | 230 (17.6) | 617 (23.3) | | |
| 2–3 drinks/day | 186 (14.2) | 793 (30.0) | | |
| 4+ drinks/day | 81 (6.2) | 266 (10.1) | | |
| First menstrual age | | | | |
| <10 | 55 (2.6) | 115 (3.8) | 14.323 | 0.002 |
| 10–12 | 1017 (49.0) | 1347 (44.4) | | |
| 13–15 | 873 (42.0) | 1386 (45.7) | | |
| >16 | 132 (6.4) | 183 (6.0) | | |
| Ever been pregnant | | | | |
| No | 233 (16.2) | 357 (12.4) | 12.215 | <0.001 |
| Yes | 1203 (83.8) | 2533 (87.6) | | |
| Currently pregnant | | | | |
| No | 25 (9.3) | 44 (4.8) | 7.709 | 0.005 |
| Yes | 243 (90.7) | 871 (95.2) | | |
| Menopause status | | | | |
| No | 1133 (54.5) | 1650 (54.4) | 0.004 | 0.951 |
| Yes | 947 (45.5) | 1384 (45.6) | | |
| History of hormone replacement use (not for birth control) | | | | |
| No | 1111 (77.3) | 2259 (78.1) | 0.355 | 0.551 |

Continued

Table 1 Continued

| Variable | No history n (weighted %) | With history n (weighted %) | χ^2 | P value |
|--------------------------------------|------------------------------|--------------------------------|----------|---------|
| Yes | 326 (22.7) | 633 (21.9) | | |
| History of thyroid disease | | | | |
| No | 1119 (77.5) | 2269 (78.4) | 0.388 | 0.534 |
| Yes | 324 (22.5) | 626 (21.6) | | |
| Current knowledge of thyroid disease | | | | |
| No | 66 (20.6) | 109 (17.8) | 1.091 | 0.296 |
| Yes | 254 (79.4) | 503 (82.2) | | |
| Thyroid status | | | | |
| Hyperthyroid | 37 (1.8) | 55 (1.8) | 11.507 | 0.003 |
| Hypothyroid | 294 (14.1) | 536 (17.7) | | |
| Euthyroid | 1751 (84.1) | 2443 (80.5) | | |

number of participants in NHANES, the incidence of hypothyroidism increased significantly along with history of use of birth control pills even after adjustments. Participants with history of 1 month–1 year (OR, 1.293; 95% CI 1.021 to 1.636; $p=0.033$), 2–10 years (OR, 1.262; 95% CI 1.022 to 1.559; $p=0.030$) and >10 years (OR, 1.555; 95% CI 1.167 to 2.072; $p=0.003$) were at higher risk of developing a hypothyroid status, adjusting for demographic covariables including age, race and education. History of taking birth control pills for more than 10 years carried a significantly higher risk of hypothyroidism (OR, 3.837; 95% CI 1.402 to 10.500; $p=0.009$) after adjusting for all considered variates including age, race, education, BMI, smoking status, alcohol use, history of thyroid disease, current thyroid disease, first menstrual age, pregnancy history, menopause status and medical use of hormone replacement. Birth control pills taking for over 10 years were burdened with higher susceptibility to hypothyroidism with or without excluding pregnant participants.

Some studies have investigated the relationship between birth control pills and hypothyroidism, but these were conducted differently. In 1978, Frank and Kay¹⁰ published the results of a cohort study of 23 000 women currently taking contraceptive pills and a similar number of controls who have never taken contraceptive pills. The study lasted for 14 months and indicated oral contraceptives exerted a protective effect against thyroid myxoedema, with an RR of 0.57. Vestergaard *et al*¹³ conducted a case–control study comprising 628 patients with autoimmune hypothyroidism and equal controls in an area with low iodine intake. The study suggested that ever use of oral contraceptives was associated with a slightly lower risk of Graves' disease in women, but not of autoimmune hypothyroidism. Another case–control study conducted by Strieder *et al*¹⁴ held opposite opinion that neither ever use (OR, 4.20; 95% CI 0.55 to 32.43) nor current use (OR, 0.89; 95% CI 0.38 to 2.10) of oral contraception was associated with hypothyroidism. In a randomised control trial, 121 healthy women were observed for TSH and thyroxine

after six cycles of use of combination oral contraceptives or progestin-only contraceptives, and both groups showed increased thyroxine-binding globulin, particularly for combination oral contraceptives.¹⁵ A retrospective study of 600 participants found use of oral contraceptives was a significant risk factor for accelerating hypothyroidism among pregnant women ($p=0.0004$).¹⁶ These conflicting conclusions may result from the limitations of follow-up duration, sample size and various confounding factors. This research especially addressed these data gaps.

Currently, birth control pills are available in different quantities. Combination oral contraceptives containing both oestrogen and progestin and progestin-only contraceptives are the two major types, which vary in their composition.³ Unfortunately, the abovementioned studies failed to provide details about birth control pills, and so did this questionnaire-based cross-sectional analysis. The prevalence of hypothyroidism in women is two to five times higher than in men, implying hormones could be involved in the disease course.^{8 17} However, the effects of progesterone or oestrogen only on thyroid function are less investigated and limited. Arafah¹⁸ included 36 postmenopausal women with or without hypothyroidism in a study and concluded that 12 weeks of oestrogen therapy could decrease thyroxine and worsen TSH in postmenopausal women with hypothyroidism treated with thyroxine. A 12-week randomised trial of oral micronised progesterone (progesterone, 300 mg/day at bedtime) conducted by Sathi *et al*¹⁹ suggested that free thyroxine (FT4) levels were higher in placebo group, but TSH and free triiodothyronine levels were comparable. Caufriez *et al*²⁰ found a reduction in TSH fluctuating with diurnal rhythmicity after a 3-week 300 mg progesterone daily administration in eight postmenopausal women. TSH concentrations kept a relatively stable daytime levels, followed by an early evening circadian rise, a nocturnal decrease and a transient rebound after final morning awakening. These studies revealed fluctuations in TSH, but are still far from the boundary value after a short

Table 2 Association between use of birth control pills and hypothyroidism

| History | Event/total (weighted %) | Unadjusted OR (95% CI) | P value | Model 1 OR (95% CI) | P value | Model 2 OR (95% CI) | P value | Model 3 OR (95% CI) | P value |
|----------------|-----------------------------|------------------------|---------|------------------------|---------|-------------------------|---------|-------------------------|---------|
| Any | 536/3034 (17.7) | 1.280 (1.104 to 1.484) | 0.001 | 1.245 (1.043 to 1.486) | 0.015 | 1.231 (0.749 to 2.025) | 0.412 | 1.190 (0.717 to 1.976) | 0.500 |
| <1 month | 21/210 (10.0) | 0.715 (0.463 to 1.103) | 0.129 | 0.758 (0.470 to 1.220) | 0.254 | 0.576 (0.210 to 1.581) | 0.284 | 0.545 (0.196 to 1.509) | 0.243 |
| 1 month–1 year | 145/864 (16.8) | 1.184 (0.961 to 1.459) | 0.113 | 1.293 (1.021 to 1.636) | 0.033 | 0.979 (0.520 to 1.842) | 0.948 | 0.965 (0.507 to 1.834) | 0.913 |
| 1–2 years | 53/329 (16.1) | 1.085 (0.795 to 1.480) | 0.606 | 1.078 (0.768 to 1.512) | 0.665 | 1.550 (0.532 to 4.509) | 0.422 | 1.514 (0.511 to 4.487) | 0.454 |
| 2–10 years | 220/1235 (17.8) | 1.329 (1.108 to 1.595) | 0.002 | 1.262 (1.022 to 1.559) | 0.030 | 1.224 (0.675 to 2.217) | 0.506 | 1.158 (0.631 to 2.123) | 0.636 |
| >10 years | 91/376 (24.2) | 1.865 (1.440 to 2.415) | <0.001 | 1.555 (1.167 to 2.072) | 0.003 | 4.025 (1.489 to 10.879) | 0.006 | 3.837 (1.402 to 10.500) | 0.009 |

Model 1: model adjusting for demographic covariables including age, race and education.

Model 2: model adjusting for individual covariables including body mass index, smoking status, alcohol use, history of thyroid disease, current thyroid disease and all variables in model 1.

Model 3: model adjusting for gynaecological covariables including first menstrual age, pregnancy history, menopause status, history of hormone replacement use and all variables in model 2.

Table 3 Association between use of birth control pills and hypothyroidism (excluding pregnancy)

| History | Event/total (weighted %) | Unadjusted OR (95% CI) | P value | Model 1 OR (95% CI) | P value | Model 2 OR (95% CI) | P value | Model 3 OR (95% CI) | P value |
|----------------|-----------------------------|---------------------------|---------|------------------------|---------|-------------------------|---------|-------------------------|---------|
| Any | 528/2916 (18.1) | 1.310 (1.122 to 1.531) | 0.001 | 1.562 (1.290 to 1.891) | <0.001 | 1.350 (0.815 to 2.238) | 0.244 | 1.356 (0.805 to 2.284) | 0.252 |
| <1 month | 21/203 (10.3) | 0.680 (0.426 to 1.086) | 0.107 | 0.898 (0.540 to 1.494) | 0.680 | 0.492 (0.170 to 1.419) | 0.189 | 0.506 (0.196 to 1.474) | 0.212 |
| 1 month–1 year | 145/835 (17.4) | 1.239 (0.996 to 1.540) | 0.054 | 1.677 (1.303 to 2.160) | <0.001 | 1.025 (0.535 to 1.966) | 0.940 | 1.011 (0.507 to 1.963) | 0.974 |
| 1–2 years | 52/320 (16.3) | 1.144 (0.829 to 1.578) | 0.414 | 1.411 (0.987 to 2.017) | 0.059 | 1.640 (0.564 to 4.767) | 0.364 | 1.694 (0.511 to 5.066) | 0.346 |
| 2–10 years | 219/1190 (18.4) | 1.329 (1.097 to 1.611) | 0.004 | 1.540 (1.227 to 1.933) | <0.001 | 1.318 (0.720 to 2.413) | 0.371 | 1.306 (0.631 to 2.446) | 0.404 |
| >10 years | 91/368 (24.7) | 1.936 (1.482 to 2.530) | <0.001 | 1.926 (1.426 to 2.600) | <0.001 | 4.861 (1.785 to 13.241) | 0.002 | 4.717 (1.721 to 12.926) | 0.003 |

Model 1: model adjusting for demographic covariables including age, race and education.

Model 2: model adjusting for individual covariables including body mass index, smoking status, alcohol use, history of thyroid disease, current thyroid disease and all variables in model 1.

Model 3: model adjusting for gynaecological covariables including first menstrual age, pregnancy history, menopause status, history of hormone replacement use and all variables in model 2.

intervention. This echoed with our study that short-term use of birth control pills is not associated with hypothyroidism. Another study revealed significantly increased TSH (3.0 mIU/L vs 2.3 mIU/L; $p < 0.0001$) and decreased FT4 (14.4 pmol/mL vs 12.9 pmol/mL; $p < 0.0001$), with elevated oestrogen and progesterone, followed by controlled ovarian hyperstimulation and especially a rapid 10-fold increase in oestrogen.²¹

Oestrogen and progesterone could also influence iodine uptake, whereas iodine deficiency is the main cause of hypothyroidism.⁸ Additionally, oestrogen could downregulate the expression of thyrotropin-releasing hormone mRNA in the paraventricular nucleus cells and upregulate the activity of thyroid peroxidase, resulting in a decrement in thyroxine synthesis,²² while progesterone could upregulate the expression of thyroglobulin, thyroperoxidase and sodium-iodide symporter mRNA in vitro.²³ Moreover, oestrogen may increase women's susceptibility to thyroid disease by activation of the phosphatidylinositol 3-kinase (PI3K) pathway in the thyroid follicular cells.²⁴ Oestrogen receptors are expressed in the majority of immune cells, and oestrogen can induce thyroid cell apoptosis, which may play a role in the high incidence of thyroid autoantibodies and autoimmune thyroid disease.²⁵ In order to minimise the confounding factors from other possible exposure of oestrogen and progestin, we calculated the primary outcomes after adjusting for first menstrual age, pregnancy history, menopause status and medical use of hormones.

In our study, a higher OR implied a higher risk of hypothyroidism as the extension of medication time. Hypothyroidism is a chronic pathophysiological process affected by inner and outer environmental balance. The internal environment homeostasis helps to process changes in oestrogen and progesterone administration through negative feedback. Therefore, a pathological thyroid will not occur due to changes in a short period of time, but will occur under long-term stimulation, such as taking birth control pills for over 10 years. The vast majority of cases of primary hypothyroidism were attributed to iodine deficiency and autoimmune disease (known as Hashimoto thyroiditis).^{7 8 26} Oestrogen and progesterone are regarded as disruptors of iodine absorption and are risk factors for Hashimoto thyroiditis. Most patients with Hashimoto thyroiditis can maintain normal thyroid function for a long time, and only a small number will show hyperthyroidism while the rest will end up with hypothyroidism.^{8 27 28}

The demographic characteristics were quite different between participants with or without history of taking birth control pills. Generally, the differences in baseline characteristics could contribute to the non-comparability of outcomes between the two groups. However, it has been reported that the prevalence of TSH abnormalities increased with older age and lower socioeconomic status.^{29–31} That is to say, the differences in demographic characteristics could be associated with the development of hypothyroid status in our study. In addition, occupation,

overweight, smoking and drinking are also significant risk factors for hypothyroidism.^{16 32} Therefore, we took all possible confounders into account by multivariate logistic regression rather than matching the variants due to the fact that the latter could reduce sample size.

Although our results are the first to reveal the significant association between history of taking birth control pills and hypothyroidism, specific medications for birth control were not available in the NHANES, which is the main limitation of our study. It is accepted that while use of oestrogen confers more susceptibility to hypothyroidism, the effects of progesterone on thyroid disorders merit further investigations. Second, overt and subclinical hypothyroidism were not distinguished in our study, because the levothyroxine supplement was adopted to most patients. Last but not the least, the cross-sectional nature of the study did not allow investigation of the causal relationship between birth control pills and hypothyroidism and this association might be affected by recall non-response bias.

In conclusion, our study used a large cohort of the US population to examine the association between history of taking birth control pills and hypothyroidism. Longer history of taking birth control pills was strongly associated with hypothyroidism, especially of more than 10 years. These findings have important implications for basic studies to determine whether there is a role for hypothyroid status and oral contraceptives.

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1. SUMMARY OF TEST PRINCIPLE AND CLINICAL RELEVANCE

The Access HYPERSensitive hTSH Assay is a two-site immunoenzymatic ("sandwich") assay, for the quantitative determination of human thyroid-stimulating hormone in human serum, using the Access Immunoassay System. A sample is added to a reaction vessel with goat anti-hTSH-alkaline phosphatase conjugate, buffered protein solution, and paramagnetic particles coated with immobilized mouse monoclonal anti-hTSH antibody. (Goat anti-mouse antibody is used to immobilize the mouse anti-hTSH antibody.) The serum hTSH binds to the immobilized monoclonal anti-hTSH on the solid phase while the goat anti-hTSH-alkaline phosphatase conjugate reacts with a different antigenic site on the serum hTSH. Separation in a magnetic field and washing removes materials not bound to the solid phase. A chemiluminescent substrate, Lumi-Phos® 530, is added to the reaction vessel and light generated by the reaction is measured with a luminometer. The light production is directly proportional to the concentration of human thyroid-stimulating hormone in the sample. The amount of analyte in the sample is determined by means of a stored, multi-point calibration curve. The major use of the hTSH assay is for the assessment of thyroid status. In patients with intact hypothalamic-pituitary function, hTSH is measured to: 1) exclude hypothyroidism or hyperthyroidism; 2) monitor T4 replacement treatment in primary hypothyroidism or antithyroid treatment in hyperthyroidism; 3) follow T4 suppression in "cold nodules" and non-toxic goiter; 4) assess the response to TRH stimulation testing. hTSH measurements are also used to identify subclinical and latent hypothyroidism or hyperthyroidism.

2. SAFETY PRECAUTIONS

Consider all plasma or serum specimens potentially positive for infectious agents including HIV and the hepatitis B virus. We recommend the hepatitis B vaccination series for all analysts working with whole blood and/or plasma. Observe universal precautions; wear protective gloves, laboratory coats. Place disposable plastic, glass, and paper (pipette tips, gloves, etc.) that contact plasma and any residual sample material in a biohazard bag and keep these bags in appropriate containers until disposal by maceration chlorination. Wipe down all work surfaces with Germicidal Disposable Wipe when work is finished.

Handle acids and bases with extreme care; they are caustic and toxic. Handle organic solvents only in a well-ventilated area or, as required, under a chemical fume hood. Reagents and solvents used in this study include those listed in Section 6. Material safety data sheets (MSDSs) for these chemicals are readily accessible as hard copies in the lab.

3. SPECIMEN COLLECTION, STORAGE, AND HANDLING PROCEDURES; CRITERIA FOR SPECIMEN REJECTION

A. Interferences:

- 1) No interference from 5-9 g/dL albumin, <10 mg/dL bilirubin or <1800 mg/dL triglycerides.
- 2) No interference from <500 mg/dL hemoglobin. Hemoglobin does

not affect the concentration of hTSH assayed.

- B. Separated serum or plasma should not remain at +15°C to +30°C longer than 8 hours. If assays are not completed within 8 hours, serum or plasma should be stored at +2°C to +8°C. If assays are not completed within 48 hours, or the separated sample is to be stored beyond 48 hours, samples should be frozen at -15°C to -20°C. Frozen samples should be thawed only once. Analyte deterioration may occur in samples that are repeatedly frozen and thawed.
- C. Fasting is not required.
- D. A minimum of 0.5 mL serum is needed for the TSH.
- E. Sample volume for individual test is 110 µL.
- F. Sample is run singly.

4. EQUIPMENT AND INSTRUMENTATION, MATERIALS, REAGENT PREPARATION, CALIBRATORS (STANDARDS), AND CONTROLS

- A. Instrumentation: Beckman Access2 Immunoassay System
- B. Materials:
 - 1) Access Immunoassay 1.0 mL Insert Cups (*Cat. #81915*)
 - 2) Access Immunoassay 3.0 mL Sample Container (*Cat. #81914*)
 - 3) Access Immunoassay Reaction Vessels (*Cat. #81901*)
 - 4) Stockwell Scientific Tubes, 13x100mm, polystyrene, (Prod #8570)
 - 5) S/P Plastic Transfer Pipette (*Cat. #P5214-10*)
- C. Reagent Preparation:
 - 1) Access HYPERsensitive hTSH Reagent Pack (*Cat. #33820*): 100 determinations, 50 tests/pack. Contains the following components:
 - R1a: Paramagnetic particles coated with goat anti-mouse IgG: mouse monoclonal anti-hTSH complexes suspended in Tris buffered saline, with surfactant, bovine serum albumin (BSA), <0.1% sodium azide, and 0.1% ProClin™300.
 - R1b: Tris buffered saline with surfactant, BSA, protein (murine, goat), <0.1% sodium azide, and 0.1% ProClin™300.
 - R1c: Goat anti-hTSH-alkaline phosphatase (bovine) conjugate in Tris buffered saline, with surfactant, BSA, protein (goat), <0.1% sodium azide, and 0.1% ProClin™300.
 - a) Provided ready to use.
 - b) Store upright at 2-10°C.
 - c) Packs must be refrigerated at 2-10°C for two hours before loading on instrument.
 - d) Unopened packs are stable until expiration date when stored as directed.
 - e) After initial use, pack is stable for 28 days at 2-10°C.
 - f) CAUTION: Sodium azide may react with lead and copper plumbing. On disposal of liquid, flush drain with large volume of water. ProClin is a potential skin sensitizer, in

- case of contact with reagent, thoroughly flush with water.
- 2) Access Substrate (*Cat. #81906*)
 - a) Lumi-Phos 530 (buffered solution containing dioxetane Lumigen PPD, fluorescer, and surfactant).
 - b) Allow substrate to equilibrate, unopened at room temperature for a minimum of 18 hours (maximum 14 days) prior to use.
 - c) Unopened substrate is stable until expiration date when stored at 2-10°C
 - d) Opened substrate on board in external fluids tray is stable for 14 days.
 - e) Substrate is sensitive to air exposure. Keep tightly closed at all times. Do not pool bottles of substrate.
 - 3) Access Wash Buffer (*Cat. #81907*).
 - a) Tris buffered saline, surfactant, 0.1% sodium azide and 0.1% ProClin 300.
 - b) Stable until expiration date when stored at room temperature.
- D. Standards Preparation: No preparation required.
- 1) Beckman Access HYPERsensitive hTSH Calibrators (*Cat. #33825*).
- E. Control Material:
- 1) Bio-Rad Immunoassay Plus Controls (Levels 1, 2, and 3) (*Cat. #371, 372, 373*).
 - a) Reconstitute each vial with 5 mL deionized water using a volumetric pipette. Replace the stopper and let control stand for 15 minutes. Before using, invert vial several times to mix.
 - b) Reconstituted control is stable for 7 days when stored at 2-8°C.
 - c) At least two levels of control should be analyzed in a 24-hour time period.
 - d) Ensure that assay control values are within the concentration ranges stated in the package insert or calculated from cumulative data at CLS.
 - e) Refer to Quality Control Flow Chart for action decision guidelines.

5. CALIBRATION AND CALIBRATION VERIFICATION PROCEDURES

- A. Calibrators: Beckman Access HYPERsensitive hTSH Calibrators (*Cat. #33825*).
- 1) Six levels of calibrator.
 - 2) Provided ready to use.
 - 3) Mix contents by gently inverting prior to use.
 - 4) Stable until expiration date when stored at 2-10°C.
 - 5) Refer to calibration card enclosed with each set of calibrators for actual concentrations.
- B. Calibration:
- 1) Calibration is required when a new lot of hTSH reagent is loaded,

when the calibration curve expires (curve stability is 28 days), or when controls are out of range.

- 2) Refer to Access2 Quick Reference Guide or Access2 “help” icon for detailed instructions on programming a calibration.

6. REPORTABLE RANGE OF RESULTS

A. Analytical Range:

- 1) 0.01 -The value of the highest calibrator (~100) $\mu\text{IU/mL}$.
- 2) A result over range high should be reported as “>100”. To obtain a numerical answer, the specimen may be diluted one volume of sample to four volumes of 0.0 Calibrator or Access Sample Diluent A (Cat. #81908). After assaying the diluted sample, multiply the printed value by 5 to obtain the reportable answer.
- 3) Beckman defines sensitivity as the lowest measurable concentration which can be distinguished from zero with 95% confidence. Sensitivity for the hTSH determination is 0.003 $\mu\text{IU/mL}$.
- 4) The literature suggests functional (clinical) sensitivity for hTSH assays is defined in terms of precision. Dose responses of 0.01-0.02 $\mu\text{IU/mL}$ with interassay (between run) Cvs of $\leq 20\%$ are considered to demonstrate “Third Generation” functional sensitivity performance.
- 5) CLS will periodically monitor low TSH reproducibility between runs by repeating patient samples. Previously repeated analysis within 1 day of samples with initial values between 0.01 and 0.03 yielded 8 results with no difference and two that differed by 0.01.
- 6) 0 is not a reportable value. Report results below 0.01 as <0.01.

7. QUALITY CONTROL (QC) PROCEDURES

- A. Blind QC Specimens are included in the samples received from NHANES.
- B. Bio-Rad Immunoassay Plus Controls levels 1, 2, 3 are assayed prior to running CDC-NHANES samples and after running CDC-NHANES samples.
- C. Acceptable Answer:
 - 1) Controls must be within ± 2 S.D.
 - 2) Refer to Quality Control Flow Chart for action decisions guidelines.

8. REMEDIAL ACTION IF CALIBRATION OR QC SYSTEMS FAIL TO MEET ACCEPTABLE CRITERIA

Remedial action for out of control conditions includes examination of the pipetting and detection equipment and examination of reagent materials. The QC parameters are compared to the patient means to look for confirmatory or disconfirmatory evidence. When the 2 2s and/or 1 3s rules are violated, samples are repeated following corrective maintenance or reagent changes.

9. LIMITATIONS OF METHOD; INTERFERING SUBSTANCES AND CONDITIONS

- A. Hemolyzed samples with up to 500 mg/dL hemoglobin have no significant interference.
- B. <10 mg/dL bilirubin has no significant interference.
- C. Lipemia has no significant interference in samples containing equivalent of 1800 mg/dL triglycerides.
- D. Samples containing 5-9 g/dL (50-90 g/dL) albumin have no significant interference.
- E. This assay has been formulated to minimize the effect of human anti-mouse antibodies or heterophile antibodies which may be present in some patient samples.
- F. TSH levels obtained during the first trimester of pregnancy or whenever very high hCG levels are present should be interpreted with caution.

10. SPECIMEN STORAGE AND HANDLING DURING TESTING

Specimens arrive frozen with dry ice. Specimens are kept frozen at -70°C until ready to analyze. Sample is thawed, mixed well by vortexing, and then transferred to sample cup or sample insert cup on the Access.

Specimen vials are returned to container and refrigerated after transfer of aliquot and double checking of Sample I.D. Specimen vial container is placed in -70°C freezer after testing is complete.

11. ALTERNATE METHODS FOR PERFORMING TEST OR STORING SPECIMENS IF TEST SYSTEM FAILS

Samples will remain in -70°C freezer until instrument is back in operation.

More details see https://wwwn.cdc.gov/nchs/data/nhanes/2011-2012/labmethods/thyrod_g_met_tsh.pdf