Changes in Serum Iodine Concentration, Urinary Iodine Excretion and Thyroid Function After Hysterosalpingography Using an Oil-Soluble Iodinated Contrast Medium (Lipiodol)

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Objective: Reports of hypothyroidism after hysterosalpingography (HSG) using lipiodol are emerging. The present study was designed to investigate the changes in serum iodine concentration (SIC), urinary iodine concentration/creatinine excretion (UI/Cr), and thyroid function before and after HSG using lipiodol.

Methods: The prospective observation study included 22 infertile euthyroid women with no previous history of thyroid disease. All underwent HSG between April 2007 and August 2008 at our institution. We examined SIC, UI/Cr, and thyroid function before HSG, and at 4, 8, 12, and 24 weeks, and 9–12 months after HSG.

Results: The median value of SIC and UI/Cr peaked at 4 weeks after HSG and remained at significantly high levels at 8, 12, and 24 weeks post-HSG compared with pre-HSG. In sync with the increase of iodine, the mean level of TSH significantly increased at 4, 8, 12, and 24 weeks post-HSG compared with pre-HSG. After 24 weeks, differences in SIC, UI/Cr, and TSH levels before and after HSG became nonsignificant. The mean value of free triiodothyronine and free thyroxine showed no significant difference at any of the time points compared with pre-HSG. Three cases (13.6%) showed transient high TSH (>5 μIU/L) with normal thyroid hormones at 4 or 8 weeks after HSG.

Conclusion: Thyroid monitoring should be conducted in the first 4–8 weeks after HSG using lipiodol and attention to thyroid dysfunction should be paid for up to 6 months after the procedure due to the possibility of excess iodine. **(*J Clin Endocrinol Metab* 100: E469–E472, 2015)**

Hysterosalpingography (HSG) is a radiographic examination of the uterine cavity and the fallopian tubes. It is frequently performed as an infertility test and involves the injection of a radio-opaque contrast medium through the cervical canal. Lipiodol, an oil-soluble iodinated contrast medium, is commonly used as it has been suggested to be a more effective therapeutic agent for infertility compared with water-soluble contrast media (1). Lipiodol contains iodine at a concentration of 480 mg/mL. The amount used is calculated based on an average of 5–10 mL lipiodol and 2.4–4.8 g excessive iodine. The recommended daily allowance for iodine in Japan is 130 μg.

Lipiodol is known to persist in the pelvic area for a long time in animal models (2). In humans, lipiodol administration can suppress the uptake of radiolabeled iodine by the thyroid gland even several months after HSG (3). Moreover, excessive amounts of iodine transiently inhibit the synthesis of thyroid hormones (known as the Wolff-

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Abbreviations: HSG, hysterosalpingography; LT4, levothyroxine; SIC, serum iodine concentration; TgAb, antithyroglobulin antibodies; TPOAb, antithyroid peroxidase antibodies; UI/Cr, urinary iodine concentration/creatinine excretion.

Chaikoff effect) (4, 5). Mekaru and colleagues (6) reported that hypothyroidism occurred after HSG using lipiodol in 214 patients, whereas another study showed that the extent of thyroid dysfunction in thyroid antibody–positive patients caused by excessive intake of iodine was more severe than those who were antibody negative (7). In addition, there have been cases of transient fetal goiter or transient neonatal hypothyroidism due to excessive iodine intake by the mother who became pregnant just after HSG with lipiodol (8, 9). In subclinical hypothyroidism, where free FT_3 and free thyroxine (FT_4) levels are normal but TSH levels are high, even a slight increase of TSH (ie, <2.5 μIU/L) can cause unexplained infertility and pregnancy complications (10). Therefore, some guidelines recommend levothyroxine (LT_4) replacement therapy for women planning pregnancy when their TSH levels are higher than 2.5 μIU/L, with or without antithyroid peroxidase antibodies (TPOAb) (11, 12).

In view of these findings, it is important to investigate the course of serum iodine concentration and thyroid function after HSG. As yet, no human longitudinal study has been conducted. The present prospective study was designed to investigate the changes in serum iodine concentration (SIC), urinary iodine concentration/creatinine excretion (UI/Cr), and thyroid function before and after HSG using lipiodol.

Subjects and Methods

Twenty-two infertile women who received HSG between April 2007 and August 2008 at our institution were enrolled onto the study. None of them had a history of thyroid disease or thyroid dysfunction at baseline. Patients who had, within the past year, undergone examination with an iodinated contrast medium (eg, cholecystography, myelography, or HSG), undergone computed tomography scan with contrast, or taken amiodarone, were excluded from the study. We examined FT_3, FT_4, TSH, SIC, UI/Cr, antithyroglobulin antibodies (TgAb), and antithyroid peroxidase antibodies (TPOAb) levels. Goiter was identified by palpation prior to HSG. Patients were asked about their amount of daily iodine intake (ie, intake of seaweed, routine use of gargle containing iodine, and any iodine-containing supplement), history of HSG, and other contrast studies, family history of thyroid disease, as well as smoking habits before undertaking HSG.

HSG was performed using lipiodol (comprising of iodine and products of ethyl esters of fatty acids obtained from poppy seed oil; TERUMO) with an iodide concentration of 480 mg/mL on day 8–9 after the onset of menstruation. The levels of SIC, UI/Cr, TSH, FT_3, and FT_4 before HSG were measured to establish baseline values, and then again at 4, 8, 12, and 24 weeks post-HSG. Five participants were re-examined at 9–12 months post-HSG. Women received LT_4 replacement therapy due to overt hypothyroidism, conceived successfully or withdrew for any reasons after HSG, were followed until when the event occurred.

Serum TSH, FT_3, and FT_4 levels were measured with an electrochemiluminescence immunoassay using ECLusys TSH, FT_3, and FT_4 (Roche Diagnostics K.K.). Laboratory reference ranges in healthy Japanese adults are: TSH, 0.50–5.00 μIU/L; FT_3, 2.30–4.30 pg/mL; and FT_4, 0.90–1.70 ng/dL. TPOAb and TgAb were measured with a RIA using TPOAb Cosmic II (500) and TgAb Cosmic II (RSR Limited), respectively. The normal reference ranges for TgAb and TPOAb are both less than 0.3 U/mL.

Measurement of urinary iodine was performed using the ammonium persulfate digestion microplate method based on Sandell-Kolthoff reaction (measuring range, 25–500 μg/L) (13). When urinary iodine of a urine sample exceeded 500 μg/L, it was diluted with purified water. The value of Cr in urine was estimated with a colorimetric enzymatic assay. All urine samples were assayed in duplicate. Urinary iodine was expressed relative to Cr (UI/Cr; μg/g Cr).

For measurement of SIC, serum specimens were diluted with water, followed by ultrafiltration to remove serum proteins. A volume of 200 μL water was added to 200 μL serum and mixed by stirring. The solution was put into a Centricut Ultramini W-50 (KURABO Industries LTD; molecular weight cut-off, 50 kDa) ultrafiltration device and centrifuged at $2000\times g$ for 10 minutes. A filtrate sample of volume 50 μL was examined with a urinary iodine measurement kit according to manufacturer's instructions. Recovery rate of various spikes of potassium iodate was 96–103%. The averages of the coefficient of variation of SIC were 7.2, 10.4, and 30% with serum iodine concentration of 510 μg/L, 231 μg/L, and 59 μg/L, respectively.

Written informed consent was obtained from all subjects, and the study was approved by the ethics committee at our institute. ANOVA and the Student t test were used to evaluate statistical significance. $P < .05$ was considered significant. Statistical analyses were performed using the JMP9 software (SAS). The result of normal distribution was described as mean values ± SD, and that of nonnormal distribution was described as a median (range).

Results

Pre-HSG clinical characteristics and examination findings of the 22 cases were as follows: age, 36.2 ± 2.45 years; iodine intake from seaweed three or more times per week, six subjects (27%); daily use of an iodine-containing gargle, none (0%); daily use of a supplement containing 150 μg iodine, four subjects (21%); history of HSG within 2 years, three subjects (13%); second degree family history of thyroid disease, four subjects (18%); goiter palpable by an experienced physician, six subjects (27%); smoking 1–9 cigarettes per day, one subject (4%), smoking 10–19 cigarettes per day, one subject (4%); FT_3, 2.81 ± 0.28 pg/mL; FT_4, 1.19 ± 0.10 ng/dL; TSH, 1.51 ± 0.64 μU/mL; SIC, 21 μg/L (range, 12–164 μg/L); UI/Cr, 330 μg/gCr (range, 1.3–11 400 μg/gCr); and TPOAb positive and/or TgAb positive, seven subjects (32%).

Of the 22 cases, none had received LT_4 replacement therapy; three conceived at 5, 10, and 12 weeks, respec-

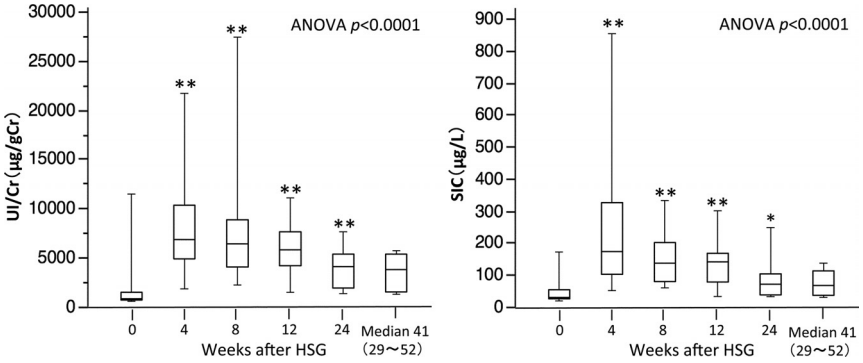

Figure 1. Changes in UI/Cr and SIC after HSG. The boxes and lines represent median UI/Cr and SIC with IQR and range. The numbers of the cases are 22, 22, 21, 18, 15, and 5 at pre-HSG, 4, 8, 12, 24, and median 41 weeks after HSG. *, $P < .05$ vs pre-HSG; **, $P < .01$ vs pre-HSG.

tively, after HSG. One was not followed up due to geographic relocation at 12 weeks after HSG, whereas three disrupted infertility treatment at their own will at 8, 8, and 12 weeks, respectively, after HSG. Six cases were re-examined at 9–12 months post-HSG.

Bilateral salpingemphraxis was not observed in any of the patients. Trapped iodine in the pelvic cavity during HSG was confirmed. On average, 6.1 mL lipiodol (range, 4.0–9.0 mL) and 2.9 g iodine (range, 1.9–4.3 g) was used for complete examination. The values of SIC and UI/Cr peaked at 4 weeks after HSG, and remained significantly high at 8, 12, and 24 weeks post-HSG compared with pre-HSG levels. Thereafter, the difference in the values lost significance (median, 41 wk; range, 29–52 wk) (Figure 1).

The amount of TSH increased significantly at 4, 8, 12, and 24 weeks post-HSG compared with pre-HSG; significance was lost thereafter (median, 41 wk; range, 29–52 wk). FT_3 and FT_4 levels showed no significant difference at any of the time points compared with pre-HSG values (Figure 2). During observation period, none had overt hypothyroidism, although three cases (13.6%) showed transient high TSH (>5 μIU/L with normal thyroid hormones at 4 or 8 weeks after HSG. The percentage of the TSH levels higher than 2.5 μIU/L was 72.7% at 4 weeks, 52.4% at 8 weeks, 61.1% at 12 weeks, 46.7% at 24 weeks post-HSG and 40.0% thereafter.

Five were positive for TgAb or TPOAb, whereas 17 were negative for both TgAb and TPOAb. The changes of TSH, FT_3, and FT_4 levels after HSG showed the same trend as above in the antibody-positive group and the antibody-negative group, respectively, but without significance.

Discussion

In the study by Mekaru, only thyroid function was measured just once several months after HSG (6). In our study, both serum thyroid function and urine iodine concentrations were evaluated prospectively over multiple time points following the exposure to lipiodol. Although the subjects of our study were euthyroid at baseline, the likelihood of abnormal thyroid function could be greater if we had included subjects with subclinical hypothyroidism. With this in mind, it is worthwhile to consider the history of thyroid disease in patients and to evaluate their thyroid function prior to HSG.

Previous reports showed that subclinical hypothyroidism was associated with unexplained infertility (14) and early pregnancy loss (15, 16). According to a recent meta-analysis, subclinical hypothyroidism in early pregnancy was also associated with a high risk of pre-eclampsia, perinatal mortality, and placental abruption (10). Although these findings remain controversial, maternal subclinical hypothyroidism or hypothyroxinemia in early pregnancy can in fact affect the offspring's psychological development (17–19).

In women who were positive for thyroid autoantibody with a TSH level higher than 2.5 μIU/L, LT_4 replacement therapy have been shown to improve pregnancy outcome (20). However, there is still insufficient ev-

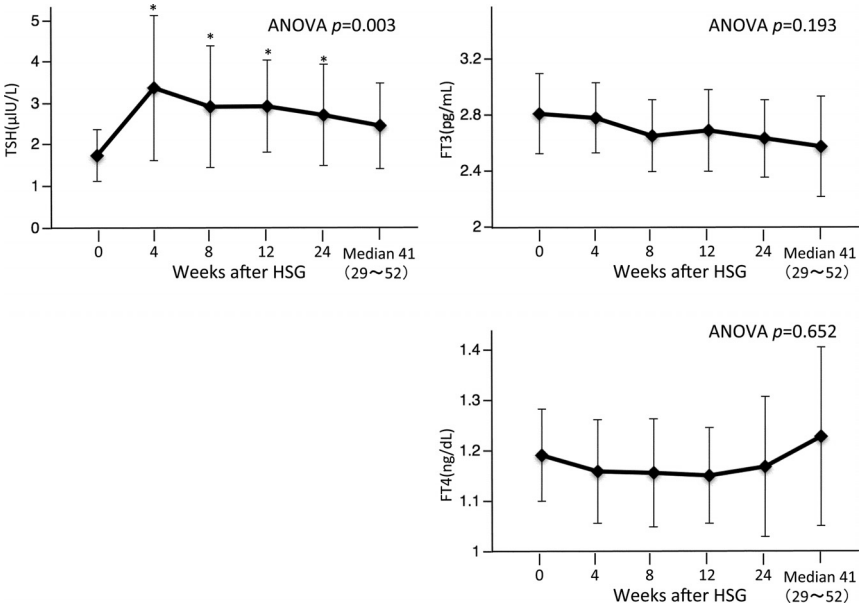

Figure 2. Changes in thyroid function after HSG. The numbers of the cases are 22, 22, 21, 18, 15, and 5 at pre-HSG, 4, 8, 12, 24, and median 41 weeks after HSG. *, $P < .01$ vs pre-HSG.

idence to support the effectiveness of such a therapy for subclinical hypothyroidism patients negative for TPOAb.

Although this is a prospective study, we could not definitively show any differences in the extent of suppression of thyroid function between thyroid autoantibody-positive and -negative patients due to the small number of positive patients available. Nonetheless, our study demonstrated that thyroid function was suppressed after HSG, which might only be applicable to subjects in iodine-adequate-to-rich areas, proposing the need to examine thyroid function of women who wish to become pregnant before and after undergoing HSG. However, our findings may not be applicable to water-soluble iodinated contrast medium regardless of administration routes (eg, computed tomography scan or HSG) because the half-life period of the oil-soluble iodinated contrast medium pool in the pelvic area is much longer.

LT_4 replacement therapy should be considered even in subclinical hypothyroidism after HSG, while keeping the possibility of infertility and adverse outcome of pregnancy in mind. We also recommend that patients who undergo HSG be monitored for thyroid dysfunction for up to 6 months because excessive levels of iodine may still be present.

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