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Original Article

The water-soluble iodinated contrast medium used for hysterosalpingography might increase the probability of development of subclinical thyroid diseases

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Abstract: Objective: Sudden exposure to high iodide levels may cause thyroid dysfunction. Although the iodinated contrast medium used for computed tomography and coronary angiography is known to alter thyroid function, the water-soluble iodinated contrast medium (ICM) used for hysterosalpingography (HSG) has not been investigated comprehensively. In the present study, we aimed to investigate the effect of the water-soluble iodinated contrast medium used for HSG on thyroid functional tests in euthyroid infertile women. Materials and methods: A total of 87 euthyroid infertile women with normal thyroid stimulating hormone (TSH), triiodothyronin (fT3) and free thyroxine (fT4) levels were included in the study. Serum TSH, fT4, and fT3 levels were measured before the study and one week, one month, and three months after HSG. Patients underwent a thyroid ultrasonography to reveal the occurrence of any change. Results: Mean TSH levels did not change significantly until the 3rd month (P=0.03). Mean fT4 levels were significantly lower (*P*<0.001) from baseline in each of the measurements performed after HSG. None of the patients had clinical hyperthyroidism or hypothyroidism during follow-up. Conclusion: The iodinated contrast medium used for HSG may be associated with the development of subclinical hyper- or hypothyroidism in euthyroid infertile women. Further study is warranted to confirm the effects of ICM on thyroid function.

Keywords: Water-soluble iodinated contrast medium, thyroid function, HSG

Introduction

Iodinated contrast media (ICM) is widely used in diagnostic work-ups. Sudden exposure to high iodide loads may disrupt thyroid hormone regulation, resulting in hypothyroidism (Wolff-Chaikoff effect) or hyperthyroidism (Jod-Basedow phenomenon) [1, 2]. Iodinated contrast media-related thyroid dysfunction has been a popular topic due to the increased use of contrast-enhanced imaging techniques in the past two decades. There have been several studies demonstrating altered thyroid hormone status following administration of ICM, particularly for computed tomography or coronary angiography [3, 4]. The Contrast Media Safety Committee of the European Society of Urogenital Radiology released guidelines that included recommendations for monitoring and managing thyroid dysfunction in patients receiving ICM. However, the report's implications for managing thyroid dysfunction were based on computed tomography, coronary angiography, and endoscopic retrograde cholangiopancreatography (ERCP) studies; data regarding the effect of hysterosalpingography (HSG) on thyroid function remains unclear [5]. Only a few studies have investigated whether thyroid dysfunction occurs in women undergoing HSG. Initially, it was suggested that altered thyroid hormone status is likely to be an indicator of post-procedural change in thyroid hormone status after HSG [6]. Another study indicated that excessive serum iodine concentrations may persist up to six weeks after administration of a lipid-soluble iodinated contrast medium [7]. How-

Table 1. Baseline characteristics of the patients

Variable	Mean ± SD n (%)
Age (years)	27.80 ± 6.00
Infertility period (years)	3.72 ± 3.82
Body mass index (kg/m^2)	25.82 ± 5.22
Waist circumference (cm)	84.45 ± 11.72
Hip circumference (cm)	100.49 ± 8.64
Baseline FSH (IU/L)	6.14 ± 1.93
Baseline LH (IU/L)	6.08 ± 3.09
Baseline E_2 (pg/mL)	46.00 ± 20.50
Prolactin (ng/mL)	13.67 ± 8.42
Total antral follicle count	17.18 ± 6.98
Number of females with PCOS	33 (37.9)
Thyroid ultrasonography	
Normal	60 (69)
Multinodular goiter	12 (13.8)
Solitary nodule	10 (11.5)
Thyroiditis	4 (4.6)
Hyperplasia	1 (1.1)

FSH: Follicle stimulating hormone, LH: Luteinizing hormone, E_2: Estradiol, PCOS: Polycystic Ovary Syndrome.

ever, data is still limited on whether water-soluble iodinated contrast medium used for HSG influences thyroid function in euthyroid infertile women.

In the present study, we aimed to assess the effect of a water-soluble iodinated contrast medium (iohexol 350 mg/mL) on thyroid function tests in euthyroid infertile women undergoing HSG.

Material and methods

The study was approved by a local institutional review board (Reference number: 20796-219-E-14-159). This prospective cohort study was performed in the Reproductive Endocrinology Department of Hitit University Corum Education and Research Hospital. The study group consisted of patients who were admitted to the hospital between June and December 2014 and underwent a HSG for radiographic evaluation of the uterine cavity and fallopian tubes. A total of 87 euthyroid infertile women with normal TSH, normal free triiodothyronine (fT4), and normal free triiodothyronine (fT3) levels were included in the study. Women with a previous history of thyroid disorder, thyroidectomy, thyroid hormone replacement therapy, radioactive iodine therapy, antithyroid medication, medication containing iodine, or usage of iodinated contrast medium in the previous three months were excluded.

Patients' demographic data, waist and hip circumferences, serum estradiol, follicle stimulating hormone (FSH), luteinizing hormone (LH), and prolactin (PRL) levels on day three of the menstrual cycle were recorded. Total antral follicle count was determined through an ultrasound examination, and the presence of polycystic ovarian syndrome (PCOS) was defined according to the 2003 ESHRE/ASRM Rotterdam criteria [6]. The hysterosalpingography procedure was performed using iohexol (Omniopaque®, 350 mg iodine/mL, Amersham Health, Cork, Ireland). Iohexol was injected through the cervical canal under fluoroscopy guidance until both the uterine cavity and fallopian tubes could be adequately visualized. The samples for serum TSH, fT4, and fT3 levels were obtained before the HSG procedure and one week, one month, and three months afterward. The serum TSH, fT4, and fT3 levels were measured by the immunochemoluminescent method (Siemens ADVIA Centaur XP Immunoassay System, Germany). A thyroid ultrasonography was performed for evaluation of thyroid morphology using a 10-MHz linear probe (5 Logic Pro, GE Medical Systems, WI, USA). The imaging was performed by the same endocrinologist.

Euthyroidism was defined as having a normal TSH (0.27-4.20 μIU/mL), fT3 (2.1-4.4 pg/ml), and fT4 (0.8-2.7 ng/dL) levels. Hyperthyroidism was defined as having a suppressed TSH (<0.27 μIU/mL) and elevated fT4 (>2.7 ng/dL) and fT3 (>4.4 pg/ml) levels. Subclinical hyperthyroidism was defined as having a suppressed TSH and normal fT4 and fT3. Hypothyroidism was defined as having an elevated TSH (>10 μIU/mL) and suppressed fT4 (<0.8 ng/dL) and fT3 (<2.1 pg/dL). Subclinical hypothyroidism was defined as having an elevated TSH (4.2-10 μIU/mL) and normal fT4 and fT3 levels.

Statistical analysis

All statistical analyses were performed using SPSS (SPSS version 19.0 Inc., Chicago, IL, USA) packaged software. Visual histograms and analytical methods (Kolmogorov-Simirnov/Shapiro-Wilk's test) were used for determina-

Table 2. Change of thyroid function during the study period

	Before HSG	At one week	At one month	At three months	*p* value
TSH (μIU/mL)	1.95 ± 0.91	1.86 ± 0.46	1.97 ± 1.11	1.88 ± 1.05	0.035*
fT4 (ng/dL)	1.31 ± 0.42	1.16 ± 0.15	1.17 ± 0.14	1.18 ± 0.16	<0.001**
fT3 (pg/dL)	3.23 ± 0.46	3.28 ± 0.27	3.22 ± 0.29	3.22 ± 0.32	0.081

TSH: Thyroid stimulating hormone, fT3: Free triiodothyronin, fT4: Free thyroxine. *According to the Bonferroni correction, four related measurements cause a total of six comparisons; thus, a *p* value less than 0.05/6=0.008 was considered significant. **In post-hoc analysis, fT4 values were significantly lower (*P*<0.001) thanbaseline in each measurement performed after HSG, whereas differences among one-week, one-month, and three-month measurements were not of significance.

Table 3. Distribution of thyroid function status between groups with different time intervals

Diagnosis	Before HSG (n)	1st week (n)	1st month (n)	3rd month (n)
Euthyroidism (TSH normal)	87	84	82	82
Hyperthyroidism (suppressed TSH, elevated fT4)	0	0	0	0
Subclinical hyperthyroidism (suppressed TSH, normal fT4)	0	1	1	3
Hypothyroidism (elevated TSH, suppressed fT4)	0	0	0	0
Subclinical hypothyroidism (elevated TSH, normal fT4)	0	2	4	2

TSH: Thyroid stimulating hormone, fT3: Free triiodothyronin, fT4: Free thyroxine.

tion of normal distribution. Continuous variables were defined by the mean ± standard deviations. Comparison of non-parametric data (TSH, fT3, and fT4) between four different measurements (before HSG, one week, one month, and three months after HSG) was performed using the Friedman test. A post-hoc test was performed using the Wilcoxon signed rank test. According to the Bonferroni correction, four related measurements cause a total of six comparisons, thus a *P* value less than 0.05/6=0.008 was considered statistically significant.

Results

Baseline characteristics of the patients are given in **Table 1**. There were 12 patients (13.8%) with multinodular goiter, 10 patients (11.5%) with solitary nodule, 4 patients (4.6%) with thyroiditis, and 1 patient (1.1%) with diffuse thyroid hyperplasia.

Comparison of mean TSH, fT4, and fT3 levels between four different measurements are shown in **Table 2**. Mean TSH and fT3 levels did not change significantly throughout the study period. There were statistically significant differences in fT4 levels among measurements done before and one week, one month, and three months after the procedure (*P*<0.001).

Table 3 shows the main study outcomes. None of the patients had hyperthyroidism or hypothyroidism during follow-up. After HSG, none of the patients had hyperthyroidism, but subclinical hyperthyroidism occurred in one patient in the first week, and this patient's thyroid status remained unchanged until the three-month follow-up. An additional two patients developed subclinical hyperthyroidism after three months. None of the patients had hypothyroidism, but subclinical hypothyroidism occurred in two patients in the first week, and these two patients remained unchanged until the third month. Two additional patients had subclinical hypothyroidism after the first month, but thyroid function returned to normal after three months in these patients.

Discussion

Our study demonstrated that there were no clinically relevant alterations in the thyroid function of euthyroid infertile women undergoing HSG using a water-soluble iodinated contrast medium; however, subclinical hypothyroidism and hyperthyroidism may occur at low rates. The Guidelines of Media Safety Committee of the European Society of Urogenital Radiology did not recommend routine monitoring of thyroid function before coronary angiography, computed tomography, or ERCP [5]. In this regard, our findings provide some evi-

dence to follow up onthyroid function in euthyroid infertile women undergoing HSG. However, the low occurrence rate found in the study's outcome precludes drawing a definitive conclusion about whether positive ultrasound findings or any other baseline features play an important role in the development of thyroid dysfunction after HSG.

Mekaru et al. [6] performed a similar study on patients receiving a lipid-soluble medium for HSG. The study included a total of 214 women, of whom 180 were in euthyroid status, 28 had subclinical hypothyroidism, and 13 had subclinical hyperthyroidism. The authors reported that hypothyroidism after HSG was significantly more common among patients with subclinical hypothyroidism than those in euthyroid status (10/28 vs. 4/180, $P<0.01$). Our results are in line with these findings; women in euthyroid status are not likely to have an increased risk of thyroid dysfunction after HSG. When taken together, it might be possible that neither lipid- nor water-soluble iodine contrast media poses any risk for thyroid dysfunction in euthyroid women. However, this must be confirmed by further studies.

Kaneshige et al. [7] reported a study on 22 infertile euthyroid women undergoing HSG using the same type of lipid-soluble agent used in the above study. Together with the thyroid function tests, the study also focused on determining serum iodine concentration and iodine concentration/creatinine excretion after HSG. The authors of the study reported that serum iodine concentration and the urine excretion ratio peaked at the fourth week after the procedure and remained high for up to 24 weeks. Similar to our findings, the study was unable to detect any clinically relevant thyroid dysfunction. However, it was the first study indicating the persistence of serum iodine levels months after HSG. Our study supported these findings. Subclinical hyperthyroidism occurred in one patient, and subclinical hypothyroidism occurred in two patients in the first week after the procedure, and these abnormalities remained unchanged until the third month.

Several experimental studies have demonstrated the negative impact of excess iodine on thyroid function. Gao et al. [9] showed that excess iodine damages thyroid follicular cells; this effect might potentially be mitigated by administration of herbs with excess iodine possessing antioxidant property. In another study, excess iodine caused increased serum thyroid hormone levels in animals, and the damage was more serious in groups eating a low-protein diet [10]. Several other potential mechanisms were proposed to underlie iodine induced thyroid dysfunction [11-13]. Iodine excess and its association with thyroid disorders is an evolving issue, and whether results from those experiments will translate into clinical relevance remains unclear.

The effect of thyroid dysfunction on pregnancy loss has also been an important concern. There has been increasing evidence of the effect of thyroid autoimmunity, as the most prevalent autoimmune state, on infertility and adverse pregnancy outcomes [14]. In one study, Su et al. [15] postulated that subclinical hypothyroidism within the first twenty weeks of pregnancy was associated with an increased risk of fetal distress, preterm delivery, poor vision development, and neurodevelopmental delay. Clinical hypothyroidism or subclinical and clinical hyperthyroidisms were also found to be associated with various adverse pregnancy outcomes.

Negro et al. [16] demonstrated that in anti-TPO-negative women, the rate of pregnancy loss was significantly higher in women with a TSH level between 2.5 and 5.0 mIU/L than for those with a TSH level below 2.5 mIU/L. The authors suggested that the upper limit of normal in TSH evaluation should be redefined to 2.5 mIU/L. Based on these studies, the need for monitoring thyroid function before and in the first trimester of pregnancy should not be ignored. However, further study is needed to establish a standardized approach for monitoring thyroid function, especially when determining the subgroup of patients at greater risk.

In a case control study by Rhee et al., the association between ICM exposureand incident thyroid dysfunction was evaluated. In this study, 178 and 213 incident hyperthyroid and hypothyroid cases (respectively) were matched to 655 and 779 euthyroid controls. The authors reported that ICM exposure is associated with the subsequent development of incident hyperthyroidism, incident overt hyperthyroidism, and incident overt hypothyroidism after a follow-up interval of 180 days or less, or more

than 180 days. Their findings are similar to our results; however, our duration of follow-up is 90 days, and we do not have a control group.

Our study had several limitations, including non-comparative design, a single-institution setting, and the short duration of follow-up. As a result, clinically relevant hypothyroidism or hyperthyroidism was not observed, while subclinical hypothyroidism and hyperthyroidism did occur. Our study could not provide any information regarding the potential contribution of various parameters, such as type of contrast medium used, pre-procedure ultrasound findings, and baseline characteristics, to the development of thyroid dysfunction. Another limitation of the study is that the presence of Graves' disease could not be excluded. Furthermore, changes in serum iodine concentration and urinary iodine excretion were not measured.We could not evaluate the deterioration of incidental thyroid function because of the absence of a control group in which aniodinated contrast medium was not used.

In conclusion, our findings suggest that ICM might increase the rate of subclinical hyper- and hypothyroidism in euthyroid infertile women. These changes in thyroid function should be taken into account for at least three months after the HSG procedure. Further studies are needed to confirm the effects of ICM onthyroid function.

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Disclosure of conflict of interest

None.

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