Gestational hypothyroidism: development of mild hypothyroidism in early pregnancy in previously euthyroid women

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Objective: To determine the proportion of euthyroid women attending a fertility practice who develop hypothyroidism in very early pregnancy (gestational hypothyroidism [GHT]), and to examine the association of GHT with exogenous gonadotropin treatment.
Design: Retrospective cohort study.
Setting: A private reproductive medicine practice.
Patient(s): All healthy women (N = 94) with infertility or recurrent pregnancy loss, TSH level <2.5 mIU/L, negative thyroid peroxidase antibodies at initial evaluation, and not taking thyroid medication, who conceived during an 18-month period.
Intervention(s): Usual fertility care; 30 women who had received exogenous gonadotropins.
Main Outcome Measure(s): Serum TSH level at the time of pregnancy detection.
Result(s): Gestational hypothyroidism (TSH ≥ 2.5 mIU/L) developed in 23 of 94 women (24%). The mean increase in serum TSH level from initial evaluation to early pregnancy was 0.45 ± 0.08 [SE] mIU/L. There was a trend toward the association of GHT with use of exogenous gonadotropins. Gestational hypothyroidism was positively associated with initial prepregnancy TSH level.
Conclusion(s): Euthyroid women may develop mild hypothyroidism in early pregnancy, especially after exogenous gonadotropin treatment. Appropriate vigilance will allow for timely levothyroxine treatment. (Fertil Steril® 2015;103:1532–6. ©2015 by American Society for Reproductive Medicine.)
Key Words: Hypothyroidism, pregnancy, infertility, spontaneous abortion, gonadotropins

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Hypothyroidism is the most common endocrinopathy in pregnant women (1). In the United States, the etiology of hypothyroidism is largely autoimmune (2). Current practice guidelines recommend levothyroxine (LT4) supplementation for pregnant women with overt or mild hypothyroidism, defined by an asymptomatic serum TSH level more than 2.5 mIU/L (2, 3). Hypothyroidism, defined by a TSH level more than trimester-specific reference ranges, has been estimated to be present in 15% of unselected pregnancies tested by a national laboratory chain (4) and has been associated with both fetomaternal and pediatric morbidity (5–9). For this reason, "aggressive case finding" before conception (2, 3) and early pregnancy aggressive case finding or universal screening for hypothyroidism (3) have been recommended, even in the absence of circulating antithyroid antibodies.

Early in pregnancy, the estrogen (E)-stimulated increase in T_4-binding globulin (10) leads to increased dose requirements in those taking LT4 before to conception (11) and may lead to gestational hypothyroidism (GHT) in untreated women without sufficient thyroid reserve (12, 13). Hypothyroidism may develop with more frequency after treatment with exogenous gonadotropins because of the associated higher E_2 levels than occur in a nontreatment cycle (12–15).

This study reports the incidence of hypothyroidism at the time of pregnancy detection in a fertility practice in women previously found to be euthyroid. We hypothesized that GHT

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is sufficiently common to inform the revision of guidelines for thyroid screening in early pregnancy in women with infertility or recurrent early pregnancy loss. We also hypothesized that gonadotropin treatment and a prepregnancy TSH level closer to 2.5 mIU/L would each increase the risk of GHT.

MATERIALS AND METHODS

At our fertility practice we reviewed the records of all consecutive patients who underwent evaluation or treatment for infertility or recurrent pregnancy loss ($\leq$3 losses) and had a new pregnancy with a positive serum pregnancy test between November 14, 2012 and May 19, 2014. Women were excluded if they had a history of autoimmune disease, were on thyroid replacement at their initial evaluation or found to be hypothyroid (TSH $>$ 2.5 mIU/L) and hence treated with LT4, or if their anti-thyroid peroxidase (TPO) level was more than 40 IU/mL. When a woman had two or more pregnancies during the study period, only the first pregnancy was included in the analysis.

All women presenting to our practice with infertility or recurrent pregnancy loss during the study period were routinely tested for TSH and anti-TPO levels. At the time of the β-hCG assays that diagnosed the index pregnancy, which were done before 6 weeks' menstrual age, all women routinely had serum TSH and free T_4 (fT_4) assays performed on site the same day. Medications used during the cycles that resulted in the index pregnancies included exogenous gonadotropins, clomiphene citrate (CC) or letrozole, metformin, and E/P for endometrial priming. Procedures resulting in pregnancy included IVF-ET, donor oocyte IVF-ET, cryopreserved ET, and IUI. Some women received no medications and/or no ET or IUI during their conception cycles.

In addition to medication and procedure use, data abstracted from clinic records included age at pregnancy diagnosis; family history of thyroid disease; prepregnant gravidity, number of prior pregnancy losses, and time in months since last pregnancy (if any); diagnosis(es) of recurrent pregnancy loss or of factors associated with infertility; results of thyroid function testing at initial evaluation (TSH, anti-TPO) and at the early pregnancy evaluation (TSH, fT4); initial β-hCG levels in early pregnancy; fetal plurality; prescription of LT4; and pregnancy outcomes (continuing pregnancy, $\geq$12 completed menstrual weeks; spontaneous abortion, loss of a confirmed intrauterine pregnancy before 12 completed weeks; biochemical pregnancy, pregnancy loss before ultrasound confirmation; and ectopic pregnancy [EP]).

The primary study outcome was the incidence of GHT, defined as a serum TSH level $\geq$2.5 mIU/L in early pregnancy. A planned secondary analysis examined the possible association of GHT with gonadotropin stimulation. The prepregnancy TSH level was examined as a possible covariate.

The β-hCG, TSH, fT_4, and anti-TPO assays were performed on an Immulite 1000 chemiluminescent autoanalyzer (Siemens). Interassay coefficients of variation (CV) were less than 10%. Data analyses were performed with JMP 10.0 Pro and SAS 9.3 software (both from SAS Systems). Statistical tests used include Student's *t* test and Wilcoxon tests for continuous variables and c^2 and Fisher's exact tests for categorical variables. Logistic regression was used to examine the association of initial TSH and GHT. Receiver operating characteristic analysis was used to search for an initial TSH threshold below which early pregnancy GHT screening might be omitted. For all analyses, $P<.05$ was taken as significant; values shown are two-tailed unless otherwise stated. The study was approved by the Institutional Review Board at Baptist Princeton Hospital, Birmingham, AL.

TABLE 1

Demographics, history, and reproductive diagnoses by use of gonadotropin stimulation.

	All women	Gonado-tropins	No gonado-tropins	*P* value
No. (%) of women	94	30 (32)	64 (68)	
Age (y)	33.0 ± 4.1	33.3 ± 4.4	32.9 ± 4.0	.67
Family history of thyroid disease	8 (9)	3 (10)	5 (8)	.72
Gravidity	1.4 ± 1.4	1.4 ± 0.3	1.3 ± 0.2	.82
Prior pregnancy loss	43 (46)	13 (43)	30 (47)	.75
No. of prior pregnancy losses	0.9 ± 1.1	0.8 ± 1.0	0.9 ± 1.2	.50
Months since last pregnancy[a,b]	18 (2–168)	20 (3–168)	14 (2–82)	.20
Diagnostic class				
Female infertility only	58 (62)	18 (60)	40 (62)	.09
Male infertility only	5 (5)	2 (7)	3 (5)	
Both partners infertile	15 (16)	8 (27)	7 (11)	
Recurrent pregnancy loss only	16 (17)	2 (7)	14 (22)	
Female infertility diagnosis[c]				
Ovulatory dysfunction	55 (59)	17 (57)	38 (59)	.80
Tubal factor	6 (6)	4 (13)	2 (3)	.08
Endometriosis	8 (9)	5 (17)	3 (5)	.10
Other female factor	8 (9)	2 (7)	6 (9)	1.00

Note: Data are shown as mean ± SD or N (%) unless otherwise stated.
[a] Among women with a prior pregnancy (N = 58).
[b] Median and range.
[c] More than one diagnosis is possible.

Hammond. Incidence of gestational hypothyroidism. Fertil Steril 2015.