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Hyperemesis Gravidarum and Thyroid: What Role for the Endocrinologist?

Brucker-Davis F[1], Rougier C[1,2], Trastour C[2], Panaïa-Ferrari P[3], Hiéronimus S[1]*

[1]Department of Endocrinology, University Hospital of Nice, France

[2]Department of Obstetrics, University Hospital of Nice, France

[3]Department of Biochemistry and Hormonology, University Hospital of Nice, France

***Corresponding author:** Sylvie Hiéronimus, Centre Hospitalier Universitaire de Nice, Université Côte d'Azur, Hôpital l'Archet 2, CHU Nice, 151 route de Saint-Antoine 06200 Nice, France

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Abstract

Objective: To characterize a population of women with Hyperemesis Gravidarum (HG) and abnormal thyroid tests.

Methods: We report 60 women with HG referred to a specialized clinic for assessment of abnormal thyroid tests early in pregnancy. They underwent thyroid ultrasound and thyroid tests (TSH, FT4, FT3, thyroid auto-antibodies) at each trimester when possible. Obstetrical and neonatal information were collected prospectively.

Results: 40% of women had a severe form of HG requiring hospitalization, 23.3% had a personal thyroid history (two Graves, six nodules, five hypothyroidisms). They were nine twin pregnancies. Ultrasound revealed 14.8% of increased thyroid volume and 26% of solid nodules. At first visit, 56 (93.3%) had a TSH<0.1mU/l. 11. 9% had at least one positive anti-thyroid antibody. 23.5% of TSH remained suppressed throughout pregnancy. HG coexisted in at least 10 cases with an underlying cause of hyperthyroidism, different from transient gestational hyperthyroidism: three active Graves' disease, five autonomous thyroid nodules, and two over-treatment with levothyroxine.

Conclusion: Hyperthyroidism is quite common in HG, but the etiology is not univocal with the possibility of underlying thyroid condition. Given the stakes of maternal hyperthyroidism and the risks of unnecessary treatment on the fetus, a precise etiological diagnosis is required, ideally by an endocrinologist, with a follow up when necessary.

Keywords: Hyperemesis gravidarum; Pregnancy; Thyroid; Transient gestational hyperthyroidism; Graves' disease; Toxic nodules

Abbreviations

HG: Hyperemesis Gravidarum; FT4: Free T4; FT3: Free T3; TPO: Anti Thyroperoxidase; Tg: Thyroglobulin; PTU: Propylthiouracyl; WA: Weeks of Amenorrhea; ART: Assisted Reproductive Techniques

Introduction

Hyperemesis Gravidarum (HG) is characterized by incoercible vomiting occurring in the first part of pregnancy and not related to other causes. Its diagnosis is clinical with additional criteria not universally accepted: dehydration, electrolyte imbalance, ketonuria and weight loss of 5% or more of body weight [1,2]. Its prevalence is estimated to 0.3 to 3% of pregnancies depending on diagnostic criteria and ethnic variation [3]. It is considered as a transient, self-limited condition [1]. However, there is a continuum between the usual mild "morning sickness" and the severe debilitating form, which requires hospitalization(s) and extends throughout pregnancy. HG is often downplayed by doctors, while the perception of women is often excruciating [4] and the true prognosis is unclear. Its physiopathology, obscure until recently, has improved with a better understanding of the role of tachykinins, such as placental endokinin or Substance P, which can cause nausea by activation of NK1R receptor in the area postrema of the brain [5].

HG is associated with gestational hyperthyroidism during the first trimester in up to 66% of cases according to Goodwin [6]. Because of its similarity of structure with TSH, hCG can bind to the TSH receptor on the thyroid, and stimulate thyroid secretion [7]. This is one of the adaptive mechanisms to the pregnancy state, allowing an increase of the thyroid hormone secretion to meet the needs of the woman and her embryo. This explains the "mirror image" between TSH and hCG concentrations at that stage of pregnancy. The prevalence of gestational hyperthyroidism increases with hCG concentrations [8], with a TSH usually suppressed when hCG is >200,000 and always when >400,000 [9]. Thus, gestational hyperthyroidism is more frequent in situations where hCG is higher (twin or molar pregnancies), or in case of molecular variants (such as reduced sialylation of hCG) [7], or exceptionally in case of mutation of TSH-receptor [10].

Currently, despite this knowledge, there is no consensus for thyroid imbalance screening in HG women, unless clinical signs of thyrotoxicosis are present [11]. We report here our experience stemming from a clinic for pregnant women with abnormal thyroid tests to discuss the role of endocrinologist in the care of this population.

Patients and Methods

Design of the study

We describe 60 women referred to our clinic dedicated to thyroid disease in pregnancy for HG and abnormal thyroid tests (TSH <0.1 mUI/l or on thyroid medication). First assessment usually occurred during the first trimester. We collected information on: personal and family medical history, obstetrical past, clinical presentation

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and treatment. Thyroid assessment included a hormonal and anti-thyroid antibody screening, and a thyroid ultrasound (see methods in reference 12). Thyroid tests were repeated at the second and third trimester, and in post-partum, when appropriate or possible. We recorded also the term at delivery, gender and weight of the newborn, mode of delivery.

Assays

As previously described [12], free T4 (FT4), free T3 (fT3), TSH, hCG, Anti-Thyroperoxidase (TPO) and anti-Thyroglobulin (Tg) antibodies were measured by chemiluminescence (ADVIA Centaur, Siemens Healthcare Diagnostics, France), and anti-TSH receptor antibodies by radio immunologic assay (Brahms Thermo Fisher, Germany). Reference ranges were established in our laboratory for fT4 and TSH during the first trimester of pregnancy (2.5 and 97.5 percentiles): fT4 11.3-19.23 pmol/l and TSH 0.1-3.23 mUI/l. The other reference ranges were provided by the manufacturer outside pregnancy: fT3 3.0-7.0 pmol/l; anti-TPO antibodies <60 UI/l, anti-thyroglobulin <60UI/l, anti TSH receptor<1.5UI/l.

Statistical analysis

Quantitative variables are expressed as medians and range. Qualitative variables are expressed as counts and percentages.

Results

Clinical characteristics are shown on (Table 1). Half the women were nulliparous. Among the women with previous pregnancies, 77% reported a personal history of HG, and 61% a family history of HG. Nine women had twin pregnancies. Eight pregnancies (13%) were induced by medically assisted procreation techniques. The mean loss of weight was 10.6% (standard deviation 5.3%, max 22.9%). 24 (40%) women needed one or more hospitalizations for rehydration and conservative care. Hypokaliemia was common (31.6%), often requiring IV supplementation. 15 women had digestive complications (eight liver abnormalities and eight pancreatitis, including two symptomatic cases). A personal history of thyroid disease was found in 14 women (two Graves' disease, five hypothyroidisms, including one after total thyroidectomy for thyroid cancer and one after lobectomy for nodule, one postpartum thyroiditis with transient hypothyroidism -untreated at first visit-, and six nodules known before pregnancy).

Thyroid ultrasound was considered normal in 32 women (55%). Thyroid volume was increased in 14.8 % of women and solid nodules were detected in 15 patients (26%), in five cases with intense intra-nodular vascularization. In addition, the thyroid was hypoechoic in six patients (10%), suggesting thyroiditis (confirmed with the presence of anti-thyroid antibodies), and cysts were found in six patients. Isolated major hyperemia was found in two women with clinical thyrotoxicosis (one with goiter) in the absence of anti-thyroid antibodies.

37% of HG women presented with mild clinical hyperthyroidism (palpitations/tachycardia and thermophobia/sweaty warm hands). Seven women (12%) received anti-thyroid medication: in four cases prescribed prior to the visit, and that we stopped, and in three cases transiently prescribed by us because of severe clinical and biological presentation (one with Propylthiouracyl (PTU) and two with carbimazole prescribed after the 1st trimester.

Table 1: Clinical characteristics of women and pregnancy complications.

	Hyperemesis
N	60
Twin N (%)	9 (15%)
Age year	31.5 (20-44)
Nulliparity N (%)	29 (48.3%)
ART N(%)	8 (13%)
Family history of thyroid disease N (%)	18 (33.3%)
Personal thyroid history	14 (23.3%)
Thyroid volume ml	11.0 (2.94-33.5)
>18 ml N(%)	8 (14.8%)
Thyroid nodules N (%)	15 (26.3%)
Maternal complication of HG	
Liver enzyme elevation	8 (13.3%)
Pancreatitis	8 (13.3%)
Hypokaliemia	19 (31.6%)
Other	1 Gayet Wernicke, 1 Mallory Weiss

Results are expressed in medians (range) or counts (%). WA: Weeks of Amenorrhea; ART: Assisted Reproductive Techniques.

Table 2: Hormonal characteristics.

	1st trimester (N=60)	2d trimester (N=52)	3d trimester (N=34)
Term WA	11 (6-16.4)	20.5 (15-27.5)	32.45 (27-37.3)
TSH mUI/l	0.04 (<0.008-3.72)	0.491 (<0.008-2.15)	0.42 (0.013-3.28)
T4L pmol/l	22.7 (11.3-77.6)	13.3 (7.09-36.1)	12.93 (8.13-20.3)
T3L pmol/l	6.35 (3.95-24.9)	4.42 (2.85-6.38)	4.48 (1-7.5)
hCG UI	196152 (60005-787200)		
singleton only	175400 (60005-399580)		
+ TPO>60 %	8.60%		
+ Anti Tg>60 %	8.70%		
+Anti TSH receptor %	6.90%		
+ thyroid antibodies %	11.90%		

Results are expressed as medians (range) or counts (%). WA: Weeks of Amenorrhea

Biological data are shown on (Table 2). 56 women (93.3%) had TSH<0.1mUI/l, suggesting biological hyperthyroidism, including 23 (40%) with undetectable TSH, at the time of the first visit. Median FT4 was 22.7 pmol/l, with 55% of values above the normal range for our laboratory. Five women were on levothyroxine supplementation because of a history of hypothyroidism, with a TSH at first visit between 0.02 and 3.72 mUI/l and FT4 between 13.2 and 19.7 pmol/l. Seven (11.9%) women had at least one positive thyroid autoantibody.

14 of 52 (27%) patients remained with a TSH<0.1mUI/l at the 2d trimester, and eight of 34 (23.5%) at the third trimester evaluation. Last, we concluded that HG coexisted in at least 10 cases with an underlying cause of hyperthyroidism, different from transient gestational hyperthyroidism: three active Graves' disease (including two de novo diagnosis), five autonomous thyroid nodules (proved in postpartum by Te99m- thyroid scan and/or surgery), and two overtreatment with levothyroxine out of five hypothyroid cases. In six

Table 3: Obstetrical and Newborn characteristics.

Obstetrical	
Term (WA)	39.1 (28.2-42)
Prematurity<37 WA	9 (15%)
Cesarean section	17 (31.5%)
Newborn	
Weight g	3150 (650-4220)
Gender	45 Females (65%)

WA: Weeks of Amenorrhea

other cases, an underlying condition was suspected but not proved; in one of those cases, the analysis of the TSH-receptor gene did not find a mutation.

Obstetrical and newborn characteristics are shown on (Table 3).

Discussion

In our series originating from a clinical practice, we found characteristics often reported in the literature for cohorts of HG women: personal or familial history of HG, a sex ratio leaning toward more female neonates [13,14], high rate of conception through reproductive techniques [13], twin pregnancies [14], digestive complications [15], including pancreatitis [16]. As expected, HG women had high levels of hCG, even when twin pregnancies were removed, compared to a historic group of euthyroid pregnant women (data not shown; ref 11).

More than half of our patients with HG were in hyperthyroid state (low TSH and high FT4). In the literature, clinical signs of thyrotoxicosis are reported absent or very rare [6,11], which is not our experience, coming from an endocrine clinic, since more than a third of our patients had such symptoms. Importantly, hyperthyroidism discovered in the context of HG is not univocal, and may reveal an underlying thyroid condition. We want to stress the interest of an endocrine expertise to establish a precise etiological diagnosis. Thyroid ultrasound is useful, as an extension of clinical examination, pending thyroid tests results, to discriminate between HG and Graves' disease or to detect potentially hyper-functioning "vascularized" nodules. In our series, all five vascularized nodules were later confirmed as toxic or pre-toxic nodules. However, in one of our cases, the markedly increased, diffuse vascularization in a patient with marked thyrotoxicosis and goiter misled us toward Graves' disease, leading us to prescribe anti-thyroid medication until the diagnosis was corrected. One key message is that underlying thyroid conditions should not be overlooked in the context of HG. In our experience, we concluded that at least ten women had another reason to develop hyperthyroidism beside the classic gestational hyperthyroidism associated to HG: three Graves, including two de novo diagnosis, five autonomous thyroid nodules, and two women with over-treated hypothyroidism who needed minor adjustment of their levothyroxine dosage. One woman with a history of Graves' disease developed transient gestational hyperthyroidism that was not a relapse of her Graves' disease. The higher prevalence of thyrotoxic nodules compared to Graves disease is somewhat unexpected in our population of young women, though the median age of 35 years for those five women was higher than the other HG women. The hormonal follow-up showing a persistent low TSH is suspicious of an underlying thyroid condition. When associated with intra-nodular hyper-vascularization, the diagnosis of toxic nodules is likely and needs to be confirmed in post-partum.

Physicians caring for pregnant women should be aware that a transient phase of hyperthyroidism is frequent in HG. Though there is no recommendation of universal thyroid screening in this population [11,17], it is useful to check thyroid tests, even more in case of personal or familial thyroid history or abnormal clinical exam. In case of suppressed TSH, it is important to set a precise diagnosis, ideally by a referent endocrinologist. A Graves'disease or a toxic nodule should be ruled out. Indeed, one major concern is to avoid inadequate anti-thyroid treatment in the usual case of transient gestational thyrotoxicosis. Thyroid tests may be followed-up at second and third trimesters, especially when thyroid ultrasound is abnormal or when thyroid antibodies are positive. Women with persisting abnormalities should be seen again within six months post-partum, to confirm or not a specific thyroid condition outside pregnancy.

Conservative management of HG is usually recommended, since many women will have a self-contained condition limited to the first half of pregnancy [17]. This includes rest, rehydration, beta-blockers, and anti-vomiting medications. In the absence of marked signs of hyperthyroidism, it is currently recommended to avoid anti-thyroid medications [17]. They have potential side effects [17], including overtreatment with the risk of fetal hypothyroidism and goiter, or birth defects, as illustrated in our short series, with the occurrence of aplasia cutis in a neonate whose mother took carbimazole starting at 15 weeks of amenorrhea. Thus, the benefit/risks of anti-thyroid medications should be weighed with regard to the risks of potential untoward event in the offspring caused by maternal thyrotoxicosis [17]. To add to those concerns, Korevaar et al based on the experience with the Generation R, have shown that subclinical maternal hyperthyroidism, as well as hypothyroidism, may impact her child further neurodevelopment [18]. Indeed, maternal fT4 concentrations (but not TSH) showed an inverted U-curve association with her child non-verbal IQ, gray matter and cortex volume on MRI [18]. A similar, though not significant trend for an inverted U curve was also observed between fT4 and verbal IQ at 5 years of age by Andersen et al [19]. Thus, given the possibility in HG of initial severe hyperthyroidism, and/or persisting subclinical hyperthyroidism throughout pregnancy, we suggest that studies should be designed testing the neurocognitive development of the offspring of HG mothers, with or without hyperthyroidism. Meanwhile, a thorough case-by-case assessment should be made in order to carefully restrict the prescription of anti-thyroid medication to markedly thyrotoxic women with or without coexisting thyroid conditions.

Conclusion

Women with HG deserve a careful assessment of their thyroid condition and a follow-up, in close collaboration with their gynecologist/obstetrician. Before down-playing the impact of this condition on the offspring, prospective studies on child neurodevelopment should be implemented.

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