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Hyperthyroidism in Gestational Trophoblastic Disease: Review Article

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ABSTRACT

Gestational trophoblastic disease (GTD) is a collection of illnesses connected to pregnancy that result from aberrant placental trophoblast growth. Some GTD patients experience the rare but possibly fatal consequence of hyperthyroidism, which calls for prompt diagnosis and treatment. There is very little research on hyperthyroidism in GTD. This review examines the epidemiology, pathogenesis, and treatment of this phenomenon. The pathogenesis of hyperthyroidism in GTD has received extensive research. The trophoblastic tissue of the placenta secretes an excessive amount of hCG, which is structurally related to thyroid-stimulating hormone and has increased thyrotropic activity. Worldwide, there are different rates of hyperthyroidism in GTD, with lower rates related to high prenatal screening uptake and early GTD discovery. We were unable to pinpoint any specific risk factors for hyperthyroidism in GTD. Although surgical removal of the uterus can definitively treat hyperthyroidism, serious consequences in GTD have been recorded, including thyroid storm-induced multi-organ failure, ARDS, and pulmonary hypertension. To stop the onset of hyperthyroidism and the difficulties that go along with it, early GTD identification is essential. Women receiving surgery for GTD should be aware of hyperthyroidism as a critical postoperative factor that needs to be adequately managed. Future research should examine the elements contributing to hyperthyroidism in GTD as this may help identify high-risk female patients early.

Keywords: [Gestational trophoblastic disease, Molar pregnancy, Hyperthyroidism, Hydatidiform mole, Pregnancy]

INTRODUCTION

The term "gestational trophoblastic disease" (GTD) refers to a diverse range of disorders connected to pregnancy brought on by an unusual growth of the placental trophoblast. The premalignant hydatidiform mole (complete and partial) and gestational trophoblastic neoplasia (GTN) are included in GTD. GTN is a category that includes invasive mole, choriocarcinoma, placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ETT) [1]. Because GTD is uncommon, has many different clinical definitions, and lacks centralized databases, it is difficult to define the epidemiology of GTD with accuracy [1, 2]. Choriocarcinoma is thought to occur in about 1/40,000 pregnancies, whereas benign GTD occurs in about 1/1000 pregnancies [3]. Epidemiological information is limited since PSTT and ETT account for just 0.2% of GTD cases [4]. In the past, GTD was linked to severe morbidity and mortality. Before the introduction of early identification and efficient uterine evacuation techniques, significant bleeding from hydatidiform moles was frequently a complication, and mortality from invasive moles was 15% due to bleeding, embolization of trophoblastic tissue, and infection. Additionally, metastatic choriocarcinoma was always lethal [5].

Today's chemotherapy and efficient uterine evacuation methods have dramatically increased survival rates, making trophoblastic tumors generally treatable. Preeclampsia, hyperthyroidism, hyperemesis, and respiratory distress are other effects of GTD [6]. Although hyperthyroidism is a rare complication of GTD, it must be identified early and treated because, when present, it can have life-threatening clinical effects. However, the early diagnosis of hyperthyroidism might be difficult due to its rarity and the low level of clinical suspicion. If the hypermetabolic symptoms are solely attributable to the trophoblastic condition, the diagnosis of hyperthyroidism may also go undiagnosed [7]. Additionally, as thyrotoxicosis can be deadly, hyperthyroidism constitutes a significant perioperative consideration given that uterine evacuation is the majority of care for hydatidiform mole and GTN [8]. Cardiovascular hyperthyroidism symptoms may be mistakenly attributed to hypovolemia during emergency surgery, making the diagnosis of hyperthyroidism challenging [9]. We are aware of very few review articles on hyperthyroidism in GTD. Individual case reports comprise most of the referenced evidence about hyperthyroidism in GTD. A thorough analysis of the existing evidence is thus urgently required. This literature review tries to summarize the data on the pathogenesis, prevalence, and consequences of hyperthyroidism in GTD.

DISCUSSION

The epidemiology of hyperthyroidism in GTD

Setting few studies have attempted to determine the prevalence of hyperthyroidism in GTD due to its rarity. This study investigated the prevalence of GTD-induced hyperthyroidism in diverse contexts. In a study conducted in England (United Kingdom), 196 individuals who received chemotherapy were examined. Four (2%) and 14 (7.2%) of the 196 patients in this group (based on TSH, FT3, and FT4) exhibited clinical hyperthyroidism, respectively [11]. The incidence of hyperthyroidism in this study may be lower than in other healthcare settings with fewer resources because GTN management in the UK is highly centralized and patients typically present early in gestation. A US study examined one of the largest gestational trophoblastic cancer registries in the US [12]. The investigators identified 172 women with partial moles and 194 with complete moles (CM) that were histopathologically confirmed (PM). Compared to women with PM, more women with CM experienced biochemical hyperthyroidism (16% vs. 4.7%). However, only 4/194 (2.1%) and 4/172 (2.3%) of the women in the CM and PM, respectively, developed clinical hyperthyroidism. Overall, this cohort's incidence of hyperthyroidism was comparable to that of the Sheffield cohort that was previously published. In their cohort of GTD patients, a 1981 South African study found a greater incidence of hyperthyroidism [13], with 15/27 (56%) having biochemical hyperthyroidism. Clinical hyperthyroidism was observed in 9/27 (33 %). The delayed identification of GTD in women in this study compared to the other studies is most likely a reason for the increased frequency of hyperthyroidism. Being a much older study, it is conceivable that early detection methods were either less developed or had lesser uptake/implementation than the current studies, leading to later GTD presentation and more excellent rates of problems related to GTD, such as hyperthyroidism. The increased incidence of hyperthyroidism in this study may be due to socioeconomic disparities and variations in healthcare resources and systems. Two investigations examined the prevalence of hyperthyroidism brought on by GTD in a Middle Eastern population. According to a study conducted in Iraq, up to 25% (10/40) of people had biochemical hyperthyroidism [14]. Clinical hyperthyroidism rates were observed in an Iranian study to be comparable to those in the UK and US studies. 10 patients (4.3%) out of 230 with a

pathologically proven CM or PM had clinical hyperthyroidism, all of them had CM [15].

Temporal trends of hyperthyroidism in GTD

There is some indication that the development of early pregnancy screening has altered the clinical patterns and presentations of GTD. We looked precisely at the pace of hyperthyroidism in GTD. In a study by Hou et al. [6], 113 cases of hydatidiform moles between 1989 and 2006 were compared to historical data between 1948 and 1975. The 'modern' group had a much lower incidence of GTD-related problems than the historical cohort, which was most likely because GTD was discovered earlier because of standard first-trimester ultrasonography and serum HCG testing [1, 6].

A Brazilian study [16] examined the medical data of women from 1988 to 2012 who had been diagnosed with a complete hydatidiform mole. They evaluated the frequency of biochemical hyperthyroidism as well as historical trends. In contrast to the earlier study by Hou et al., women with GTD had a much higher frequency of hyperthyroidism (0.69 % in 1988–1992, 0.68 percent in 1998–2002, and 3.86 percent in 2008–2012). Notably, this center's most recent rates of biochemical hyperthyroidism (2008–2012) were lower than those reported in the other investigations. The steady rise in rates over time likely reflects modifications to the GTD management system. When a patient presented with overt clinical hyperthyroidism or when the uterus was noticeably enlarged (> 16 cm) before 2010, the center solely evaluated the patient for hyperthyroidism. But starting in 2010, all patients underwent routine thyroid cancer screenings [16]. The difference between hyperthyroidism in whole moles and partial moles illustrates how hyperthyroidism in GTD can be missed in the absence of routine biochemical screening. In a Turkish cross-sectional study [17], thyroid function was evaluated in women with GTD, and outcomes in PM and CM were compared. When compared to women with a pathologically confirmed diagnosis of PM, women with CM had greater total T4 (mean 17.04 vs 2.04), higher free T4 (mean 2.15 vs 1.64), and lower TSH (mean 0.28 vs 0.91). In contrast to women with partial moles, patients with complete moles were older and had more pregnancies. This study did not evaluate the clinical state of the ladies; it only focused on biochemical hyperthyroidism. The results of the 2015 US study [12] already mentioned corroborate the finding of a greater incidence of biochemical hyperthyroidism in CM.

Ethnicity and the risk of hyperthyroidism in GTD

We also explored the possibility that ethnicity could increase the risk of hyperthyroidism in GTD patients. Only one retrospective study from 2016 investigated the impact of ethnicity on the clinical characteristics of entire moles. A total of 167 patients were examined; of these, 96 (57%) were White, 22 (15%) Asian, 22 (13%) Hispanic, and 24 (14%) Black. There was no statistically significant link between race or ethnicity and the prevalence of hyperthyroidism [18].

Pathophysiology of hyperthyroidism in GTD

Numerous research has looked into the pathophysiological processes behind hyperthyroidism in GTD. The effects of thyroid stimulating hormone (TSH) or thyroid stimulating antibodies (as in Graves' disease) alone cannot account for the hyperthyroid state in GTD. The hyperthyroidism also resolves quickly after removing the hydatidiform mole or trophoblastic tumor. These results indicate that the thyroid stimulating factor originates mainly from the trophoblastic tissue [19]. The critical mediator of hyperthyroidism in GTD is hCG, which has thyrotropic actions [20–22]. This results from "spillover effect," in which a hormone interacts with a receptor

for a different hormone and has effects that depend on the particular receptor type that is activated [19]. This "spillover effect" can happen under a few circumstances.

First structural similarities between hCG and TSH exist. The two subunits (alpha and beta) that makeup hCG are linked noncovalently to form a heterodimer. While the beta subunit of hCG is comparable to yet sufficiently different from TSH to give it its biological functions, the alpha subunit is nearly identical to TSH [23]. Due to the biological similarities between hCG and TSH, hCG can act on thyroid membranes by binding to the TSH receptor. Additionally, when the hormone is present in excess in pathological conditions, such as GTD, the likelihood of a clinically significant "spillover effect" increases. It is believed that in healthy pregnancies, hCG's affinity for the TSH receptor and thyrotropic efficacy are sufficiently low for any "spillover effects" to be insignificant [19]. This theory is supported by the fact that blood hCG and thyroid hormone levels are highly correlated [24]. The degree of clinical hyperthyroidism may be predicted by serum hCG levels, which is significant [11]. Numerous investigations have also shown that the biological characteristics of the hCG secreted by hydatidiform moles and GTN differ from those of women carrying normal pregnancies. The hCG isoform produced by hydatidiform moles exhibited much higher thyrotropic activity than hCG preparations from normal pregnancy, according to Yoshimura et al. (1994) [25]. When comparing the prevalence of hyperthyroidism in women with normal pregnancy, hydatidiform mole, and choriocarcinoma, Kato and colleagues (2004) [26] concentrated on those whose hCG serum levels were less than 100,000 IU/l. The scientists discovered that individuals with choriocarcinomas had a considerably greater frequency of hyperthyroidism (4/7; 57%) compared to those with a normal pregnancy (5/28; 17.9%%), which supported the idea that the biological properties of the hCG produced by choriocarcinomas may be altered. However, patients with choriocarcinoma had considerably greater free beta-hCG levels than those with normal pregnancies. Free beta hCG may be a possible confounder even though its thyrotropic effect in the presence of choriocarcinoma is unknown. The pathophysiology of hyperthyroidism in GTD may be supported by excessive secretion of a variant hCG molecule, according to these findings.

Outcomes and complications of hyperthyroidism in GTD

The effects and side effects of hyperthyroidism in GTD have only been recorded in case reports and case studies. Both full and partial moles have been associated with the development of thyroid storms [27, 28]. Thyroid storms are severe thyrotoxicosis clinical symptoms that might result in organ decompensation. Due to the lack of commonly available objective grading systems, calls for a high degree of suspicion and clinical knowledge [28]. The fact that patients with hyperthyroidism in GTD typically do not display conventional Graves' disease characteristics, such as ophthalmoplegia and pretibial myxoedema, is crucial for the diagnosis. This is probably because trophoblast-induced hyperthyroidism lasts for a shorter period [27]. In addition to cases where thyroid storm developed after surgical evacuation of the molar pregnancy, some patients develop or present with clinical manifestations of thyroid storm after admission [25]. This is likely because of the interaction of high hCG levels, stress from the surgical procedure, and hypovolemic state from blood loss. This underlines the significance of thorough anesthesia considerations [19] and pre-operative thyroid function testing [25]. The course of treatment for hyperthyroidism in GTD is similar to that for primary thyroid pathologies. Most individuals with clinical hyperthyroidism will benefit from supportive treatment, such as beta-blockers, and anti-thyroid drugs [11]. The final form of treatment for

thyrotoxicosis, mole evacuation, also has a quick recovery time. Nearly all patients become euthyroid after surgery, no longer exhibit clinical signs of hyperthyroidism, and do not need additional drugs in the weeks following discharge. A few cases of severe hyperthyroidism in GTD have been documented that were unresponsive to medical treatment plans and required the use of therapeutic plasmapheresis to quickly get the patients ready for surgery [26-28]. Thyroid hormone levels persisted high despite therapy with propylthiouracil and propranolol in one instance of the hydatidiform mole [28]. Day 14 saw a recurrence of hyperthyroidism despite including cholestyramine and inorganic iodine. Another partial mole instance has been described [28]. Despite a 10-day course of treatment with propylthiouracil and propranolol, as well as the addition of inorganic iodine and dexamethasone, thyroid hormone levels remained elevated. The second patient furthermore developed increased vaginal bleeding. Rapid hormonal and hemodynamic management were essential in these two cases because immediate surgery was recommended since preoperative thyrotoxicosis is linked to surgical morbidity and mortality [27], due to the elimination of excess thyroid hormone linked to blood proteins, plasmapheresis treatment in both cases caused a rapid drop in thyroid hormone levels. Thus, patients who either do not respond to medical therapy or experience adverse effects from medicine may think about therapeutic plasmaphoresis. Plasmapheresis may be associated with problems like pruritus, urticaria, hypotension, coagulopathy, and anaphylaxis, yet these two patients did not have any adverse side effects following the therapy [26]. ARDS, pulmonary edema, pulmonary hypertension, and abrupt renal failure are only a few of the severe consequences reported in case studies although the results of hyperthyroidism in GTD are generally positive.

Discuss findings of your study with relevant reasoning along with proper citations/references.

CONCLUSION

A potentially fatal complication of GTD is hyperthyroidism. The structural similarity of hCG and TSH, elevated amounts of hCG secreted by trophoblast in GTD, and higher thyrotropic activity of hCG in GTD can all be used to explain the pathophysiology of trophoblast-induced hyperthyroidism. Due to the higher levels of hCG produced in CM compared to PM, biochemical hyperthyroidism is more likely to be seen in CM. Implementation and adoption of early antenatal screening are anticipated to have a significant impact on the incidence and prevalence of hyperthyroidism. Fewer women are presenting with gestational diabetes later in pregnancy as a result of the rising usage of first trimester ultrasonography and serum hCG testing together with early therapy, which has decreased the frequency of identifying typical GTD signs including hyperthyroidism. The prevalence of hyperthyroidism in GTD may also indicate socioeconomic inequalities in the availability of healthcare resources and healthcare systems. Future research should confirm that there is inadequate information to determine whether ethnicity is a risk factor for hyperthyroidism in GTD.

Given that hyperthyroidism can cause severe morbidity and mortality, it is crucial to identify and treat it. Anti-thyroid drugs can effectively control the majority of hyperthyroidism cases in GTD, and plasmapheresis may be an alternative therapeutic option in patients unresponsive to conventional therapy or who need urgent surgery. The only effective therapy option for hyperthyroidism in GTD is surgical uterine evacuation. After surgery, most patients will be euthyroid and won't need any further antithyroid medication. A thorough anesthetic work-up for hyperthyroidism is crucial before surgery, nevertheless. Hemodynamic state and

thyroid function should be optimized ahead of surgery to reduce the risk of problems in GTD patients who have hyperthyroidism.

Perioperative anesthesia management must be carefully planned [22]. The lack of observational research precluded a quantitative investigation (meta-analysis) of our findings. Additionally, there was a lot of variation throughout the studies, especially regarding the case definition for GTD, the diagnostic standards for hyperthyroidism, and the variety of patient demographics (e.g. timing of presentation, pre-existing comorbidities and type of GTD). Numerous observational studies' retrospective design leaves them vulnerable to information bias since study variables and results could be misclassified.

Furthermore, it is challenging to confirm the precision and thoroughness of recorded data. An example of selection bias would be excluding patients who lacked data on biochemical indicators of thyroid function. Conclusion We have demonstrated in this review that hyperthyroidism is an uncommon but significant clinical feature in GTD. Despite being very curable, it can cause significant morbidity and mortality. Larger observational studies are required to further understand this illness, increase early identification, and lessen its effects.

Declaration by Authors

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