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HYPERTHYROIDISM SECONDARY TO GESTATIONAL TROPHOBLASTIC DISEASE : A LITERATURE REVIEW

I Gede Bagus Sentosa*
**T.C Hillers General Hospital, Maumere, Indonesia*

Corresponding Author:
igbsentosa@gmail.com

Abstract
Gestational trophoblastic disease (GTD) is a rare form of pregnancy-related cancer that is effectively treatable. GTD is accompanied by the potentially fatal complication of hyperthyroidism. We created a review consisting of five case reports. This case report was conducted on women who became pregnant when they were >35 years old. They showed consistent laboratory results, in which there was an increase in hCG levels. TSH and thyroid stimulating antibodies cannot account for the hyperthyroidism associated with GTD. The source of the thyroid stimulating agent is trophoblastic tissue. The thyrotropic effects of β-hCG mediate GTD hyperthyroidism. Other research examined the prevalence of hyperthyroidism in women with normal pregnancy, hydatidiform mole, and choriocarcinoma who had β-hCG serum levels below 100,000 IU/ml. Early prenatal screening may significantly reduce hyperthyroidism rates. Thyroid hormone synthesis inhibitors treat hyperthyroidism in pregnancy. Thioamides, propylthiouracil (PTU), and methimazole (MMI) are the most prevalent U.S. antithyroid medications (ATD). Plasmaphoresis may be an option for people who are resistant to therapy or need emergency surgery. GTD can cause fatal hyperthyroidism. Anti-thyroid medicines can handle most GTD hyperthyroidism. Surgery may be a possibility for patients refractory to medical treatment.

Keyword: *β-hCG; Gestational trophoblastic disease; Hyperthyroidism*

INTRODUCTION

Gestational trophoblastic disease (GTD) is an uncommon form of pregnancy-related malignancy that can be treated successfully. The uterus is the site of the growth of GTD cells; the formation of the disease takes place in the trophoblast layer of the uterus, which initially begins with cells that emerge during pregnancy and have a tendency to proliferate uncontrollably. Histologically speaking, GTD include invasive and metastatic moles, full and partial hydatidiform moles, choriocarcinoma, placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ETT).[1–3]

GTD is a relatively uncommon ailment, occurring in around 110 to 120 out of every 100,000 pregnancies in both the United States and Europe. Gestational trophoblastic disease as a whole is a rare condition. The vast majority of cases involve molar pregnancies, which are more common among women of Asian, Hispanic, and Native American ancestry. Choriocarcinoma is diagnosed in around two to seven pregnancies out of every one hundred thousand pregnancies in the United States. The percentage of people who have GTD in different countries varies widely around the globe.[3–5]

A history of past hydatidiform mole pregnancies, ethnicity, and maternal age beyond 40 years are also risk factors for choriocarcinoma. Choriocarcinoma can develop after any pregnancy, although the risk is significantly increased after a complete molar pregnancy as compared to the risk following other types of pregnancies.[6,7] After a complete hydatidiform mole, the risk of developing choriocarcinoma is approximately 15–20%, although the risk is significantly lower (less than 5%) after a partial mole.[1] Some patients with GTD develop hyperthyroidism, a rare but potentially life-threatening complication requiring early detection and management.[8]

Hyperthyroidism, despite being a rare complication of GTD, can have life-threatening clinical consequences, necessitating early detection and treatment. However, the early diagnosis of hyperthyroidism can be difficult due to its rarity and clinicians' lack of suspicion. If the hypermetabolic symptoms are merely attributed to trophoblastic disease, the diagnosis of hyperthyroidism may also be missed. Moreover, since uterine evacuation is the mainstay of treatment for hydatidiform mole and GTN, hyperthyroidism is a crucial perioperative consideration, as thyrotoxicosis can be fatal.[8–11] The aim of this research is to assess the hyperthyroidism secondary to Gestational trophoblastic disease.

METHODS

By reviewing the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 criteria, the author of this study ensured that it met all requirements and was up to date. This is performed to ensure that the investigation's findings are accurate. This investigation discovered hyperthyroidism caused by trophoblastic disease of pregnancy. The most effective method to accomplish this is to review previous research on the topic. The purpose of this post is to demonstrate the significance of the issues that have been raised.

Before participating in the study, researchers were required to meet the following requirements: 1) To be considered for publication, the paper must be written in English and its primary focus must be on the treatment of hyperthyroidism due to trophoblastic disease during pregnancy. 2) This assessment takes into account works published after 2018, but before the evaluation period. Editorials, applications without a DOI, previously published review articles, and entries that are nearly identical to previously published journal papers are examples of research that cannot be published.

We used " hyperthyroidism secondary" and "gestational trophoblastic disease" as keywords.The search for studies to be included in the systematic review was carried out from May, 28th 2023 using the PubMed and SagePub databases by inputting the words: *("hyperthyroidal"[All Fields] OR "hyperthyroidic"[All Fields] OR "hyperthyroidism"[MeSH Terms] OR "hyperthyroidism"[All Fields] OR "hyperthyroid"[All Fields] OR "hyperthyroids"[All Fields] OR "hyperthyroidisms"[All Fields]) AND ("neoplasm metastasis"[MeSH Terms] OR ("neoplasm"[All Fields] AND "metastasis"[All Fields]) OR "neoplasm metastasis"[All Fields] OR "secondaries"[All Fields] OR "secondary"[MeSH Subheading] OR "secondary"[All Fields]) AND ("gestational trophoblastic disease"[MeSH Terms] OR ("gestational"[All Fields] AND "trophoblastic"[All Fields] AND "disease"[All Fields]) OR "gestational trophoblastic disease"[All Fields])* used in searching the literature.

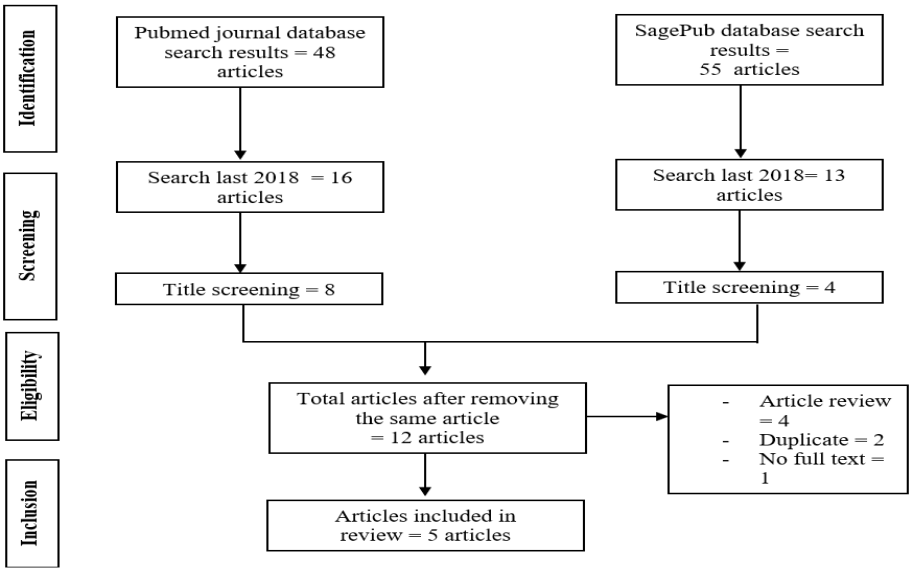

Figure 1. Article search flowchart

Each study's eligibility was determined based on its abstract and title. They subsequently consulted historical archives. This result was the result of numerous investigations employing the same methodology. Unpublished English contributions are required. Only studies meeting inclusion criteria were included in the systematic review. This restricts the search results. Insufficient research results are not examined. The analysis will follow next. The paper revealed the identities, authors, publication dates, location, study activities, and parameters of the participants. Endnote removed duplicate results from the list of search results. Two reviewers examined the article titles and abstracts that were pertinent. Their entire papers were initially evaluated for eligibility and data collection. GWG and other health concerns have been examined in reviews, animal studies, conference papers, and studies. During deliberation, the justices reached a consensus. Before deciding which papers to analyze in greater detail, each author reviewed the titles and abstracts of each publication to determine which studies to analyze in greater depth. Then, we will investigate all papers that meet the review's inclusion criteria and merit inclusion. Then, based on what we have learned, we will choose which articles to include in the review. In this manner, both the articles to be reviewed and those to be investigated are chosen.

RESULT

A case report by Grzechocinska (2021) with a hydatidiform mole caused hyperthyroidism in a 47-year-old woman. Drugs that stabilize thyroid hormones were recommended for patient preparation. Thyroid hormone levels gradually normalized after hydatidiform mole excision. The trophoblast secretes β-hCG, a hormone. TSH receptor affinity is caused by β-hCG partial structural homology. β-hCG blood levels increase with trophoblast weight. Hyperthyroidism may accompany gestational trophoblastic illness. Despite its frequent description, the risk of thyroid storm makes it unavoidable.[13]

Bettina, et al (2020) conducted a study with 2 patients. Based on thyroid function test results, both patients were diagnosed with gestational trophoblastic disease (GTD) associated with hyperthyroidism due to their elevated β-hCG levels and ultrasound evidence of molar pregnancy. Case 1 had lower levels of β-hCG and free T4 than Case 2, but a clinical evaluation of Case 1 revealed a severe illness with a more convoluted course and the development of a thyroid storm. Case 2's β-hCG levels were nearly double those of Case 1, but she was stable and her levels declined much more rapidly, reaching and remaining undetectable.

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size	Result
Grzechocinska, 2021[13]	Poland	Case report	One patient	Thyroid hormone levels gradually normalized after hydatidiform mole excision. The trophoblast secretes hCG, a hormone.TSH receptor affinity is caused by hCG partial structural homology. hCG blood levels increase with trophoblast weight. Hyperthyroidism may accompany gestational trophoblastic illness. Despite its frequent description, the risk of thyroid storm makes it unavoidable.
Bettina, 2020[14]	South Africa	Case report	Two patients	These cases illustrate that the beta-hCG levels do not necessarily have a correlation with the severity of the disease or the patient's prognosis in GTD patients.
Guzman, 2021[15]	United State of America (USA)	Case report	One patient	She was thought to have thyrotoxicosis because of a molar pregnancy, and a thyroid storm was feared. Taking care of her was hard because she had a mental health problem and bacteraemia. She was given a beta-blocker, an antithyroid drug, and antibiotics through an IV. She had a suction dilation and curettage (D&C) procedure, which was not hard. A few days later, her problems went away. At a follow-up visit, she was still showing no signs of illness and felt fine.
Santos, 2022[16]	United State of America (USA)	Case report	One patient	This case demonstrates how important it is to examine GTD as a possible cause of thyrotoxicosis in perimenopausal women, particularly when there are no symptoms that suggest primary thyroid illness.
Simes, 2018[17]	United State of America (USA)	Case report	One patient	This case describes the unusual occurrence of a full hydatidiform mole that caused hyperthyroidism and a concomitant detection of a mature cystic teratoma. Both of these conditions are extremely rare. It also emphasizes the significance of monitoring β-hCG levels after a complete molar pregnancy because of the elevated risk of choriocarcinoma that is associated with such pregnancies.

Guzman, et al (2021)[15] showed a case report with G8P7, a 49-year-old lady with an unplanned pregnancy, had severe vaginal bleeding and abdominal discomfort for one week. Molar pregnancy was suspected by vaginal ultrasound and high hCG. On her admission night, the endocrinology team was consulted for hyperthyroidism. Laboratory results indicated hyperthyroidism. The patient had thyrotoxicosis from molar pregnancy and a thyroid storm was suspected. Her mental illness and bacteraemia complicated her care. Beta-blocker, antithyroid, and intravenous corticosteroids were prescribed. Her symptoms resolved a few days following a simple suction dilation and curettage (D&C). At follow-up, the patient was asymptomatic and healthy.

Other case showed a50-year-old gravida 2 para 2 perimenopausal lady went to the emergency department with significant acute lower abdomen discomfort and abnormal uterine bleeding for one month. She also complained one-week irregular perspiration and palpitation and three-month amenorrhea. Serum β-hCG levels were high, and abdomen ultrasonography showed a "snow-storm" uterus, suggesting GTD. Laboratory tests showed suppressed TSH and elevated free thyroxine and free triiodothyronine. She developed a hydatidiform mole following surgery. After three months, her thyroid function normalized without antithyroid medicines.[16]

Simes (2018)[17] talk about a 53-year-old African American woman with a history of hyperthyroidism caused by a full hydatidiform mole and a mature cystic ovarian teratoma that was found at the same time. She felt sick, threw up, was worried, gained weight, had stomach pain, and had a b-hCG level of more than 450,000mIU/mL. Her symptoms went away after she had a total abdominal hysterectomy with bilateral salpingo-oophorectomy. In the months after the surgery, b-hCG levels went up a little bit and lung tumors were found. The acute signs of hyperthyroidism were treated with propranolol and methimazole.

DISCUSSION

A Sheffield GTD center studied 196 chemotherapy-treated patients. 14 (7.2%) of these 196 individuals exhibited biochemical hyperthyroidism (TSH, FT3, and FT4), while four (2%) had clinical hyperthyroidism.[18] One of the largest US gestational trophoblastic cancer registries was show 194 women had CM and 172 had PM. More women with CM had biochemical hyperthyroidism than PM (16% vs 4.7%; $p < 0.001$). 4/194 (2.1%) CM women and 4/172 (2.3%) PM women had clinical hyperthyroidism. This cohort had similar hyperthyroidism rates to the Sheffield cohort.[19]

Thyroid function in women with GTD and compared the findings to PM with CM. When compared to those with pathologically diagnosed PM, women with CM had lower TSH (0.28 vs 0.91; $p = 0.011$), higher free T4 (2.15 vs 1.64; $p = 0.042$), and greater total T4 (17.04 vs 2.04; $p = 0.028$). It is worth noting that patients with complete mole were older and had more pregnancies than women with partial mole. The women's clinical state was not assessed in this study, which solely looked at biochemical hyperthyroidism.[12] The discovery of greater incidence of biochemical hyperthyroidism in CM supports the findings of the previously mentioned 2015 US study.[20]

Several research have investigated GTD hyperthyroidism's pathophysiology. TSH and thyroid stimulating antibodies (as in Graves' disease) cannot explain GTD's hyperthyroidism. Hyperthyroidism resolves quickly after hydatidiform mole or trophoblastic tumor resection. The thyroid stimulating agent comes from trophoblastic tissue. B-hCG mediates GTD hyperthyroidism by its thyrotropic effects.[18] "Specificity spillover" occurs when one hormone interacts with the receptor of another hormone, eliciting consequences based on the receptor activated.[8,9]

β-hCG and TSH are structurally similar. β-hCG is a heterodimer of alpha and beta subunits linked noncovalently. hCG's alpha subunit is nearly identical to TSH, but its beta subunit is different enough to give it biological features. β-hCG affects thyroid membrane TSH receptors due to its similarity to TSH. Pathological hormone excesses like GTD enhance the likelihood of a clinically severe "spillover effect." Normal pregnancies have minimal β-hCG affinity for the TSH receptor and thyrotropic potency, hence "spillover effects" are negligible. β-hCG levels correspond with thyroid hormone levels.[8,9,14]

Several investigations have shown that β-hCG released by hydatidiform moles and GTN differs from β-hCG in normal pregnancies. β-hCG from hydatidiform moles had considerably more thyrotropic activity than β-hCG from normal pregnancy. Other study evaluated hyperthyroidism rates in women with normal pregnancy, hydatidiform mole, and choriocarcinoma with β-hCG serum levels below 100,000 IU/l. The scientists showed that choriocarcinoma patients were more likely to have hyperthyroidism than normal pregnancy, suggesting that hCG released by these tumors may have changed biological features.[8,9]

Thyroid hormone synthesis inhibitors treat hyperthyroidism in pregnancy. Thioamides, propylthiouracil (PTU), and methimazole (MMI) are the most prevalent U.S. antithyroid medications (ATD). Outside of North America, carbimazole, a methimazole prodrug, is utilized.[21] All hyperthyroidism patients were treated with PTU. Hepatoxicity can cause liver failure and transplantation. If tolerated, methimazole is used more often. In early pregnancy, methimazole and carbimazole can cause a rare embryopathy that causes aplasia cutis, abdominal wall defects, esophageal atresia, choanal atresia, ocular abnormalities, urinary tract abnormalities, and circulatory malformations.[22,23]

Patients switch to methimazole after organogenesis is complete in the first trimester. This transition prevents hepatotoxicity. PTU causes mild birth abnormalities that may not be detected until years later. Unilateral kidney dysgenesis, situs inversus, and cardiac outflow tract abnormalities are birth disorders. Unlike methimazole embryopathy, which causes many abnormalities, these defects usually occur alone. Despite teratogenicity, uncontrolled overt hyperthyroidism can harm maternal health and cause fetal loss, therefore antithyroid medicines are frequently necessary. ATDs cross the placenta and treat maternal TRAb-induced fetal hyperthyroidism.[22,23]

ATDs can overcorrect fetal hyperthyroidism even in euthyroid mothers, causing hypothyroidism. Thus, treatment aims to utilize the lowest dose of antithyroid medication with a TSH target slightly lower than the reference range and a maternal free T4 at the high end of normal. TSH normalization indicates that the fetus is receiving too much ATD. PTU and methimazole are excellent antithyroid medications, however their pharmacokinetics demand different doses. A 1:20 methimazole/PTU ratio can be utilized to switch. Due to its shorter half-life than methimazole, PTU is dosed 100 to 300 mg three times a day.[22,23]

KI can also cure moderate hyperthyroidism. Pregnancy studies are scarce. Japan has had the most success treating moderate hyperthyroidism during pregnancy with few side effects. KI's efficacy cannot be generalized because Japan consumes more iodine than most countries. However, mild hyperthyroidism ladies who cannot handle ATDs may choose KI. Surgery is best done after pregnancy. Surgery may be an option for women who cannot control hyperthyroidism with high dosages of ATDs, have ATD allergies, or are noncompliant. Large goiters that compress can be surgically removed. In pregnancy, complete or partial thyroidectomy is safest in the second trimester.[22,24]

Beta-blockers like propranolol can treat symptoms in pregnancy until euthyroidism is achieved. Fetal anatomy ultrasounds can detect thyroid anatomy and function in Grave disease patients. Between 18 and 22 weeks, complete this survey. Enlarged thyroid, intrauterine growth limitation, hydrops, accelerated bone maturity, fetal tachycardia, goiter, oligohydramnios, or heart failure may indicate thyroid dysfunction. To assess prenatal and neonatal hyperthyroidism risk, TRAb should be remeasured at 18–22 and 30–34 weeks.[25] Professional societies disagree, however TRAb levels larger than three times the upper limit of normal or a history of a newborn with a thyroid issue may warrant further monitoring.[23]

CONCLUSION

GTD can cause fatal hyperthyroidism. The structural homology of hCG and TSH, high trophoblast-secreted hCG levels in GTD, and increased thyrotropic activity of hCG explain the pathophysiology of trophoblast-induced hyperthyroidism. Early prenatal screening may drastically reduce hyperthyroidism rates. Plasmaphoresis may be a possibility for patients refractory to medical treatment or requiring urgent surgery. Anti-thyroid medicines can handle most GTD hyperthyroidism.

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