CASE REPORT

Hyperemesis Gravidarum with Gestational Transient Thyrotoxicosis Inducing Thyrotoxic Periodic Paralysis in Diabetes Mellitus and Hypertension: A Case Report

Yovita Gotama[1*], Dewi Catur Wulandari[2]

1 Intern General Practitioner, Department of Internal Medicine, Wangaya Regional Hospital
2 Endocrinologist, Department of Internal Medicine, Wangaya Regional Hospital

*Corresponding author:
Yovita Gotama, MD.
Intern General Practitioner, Department of Internal Medicine, Wangaya Regional Hospital, Denpasar, Bali, Indonesia.
Email: yovita.gotama@gmail.com

ABSTRACT

Hyperemesis gravidarum (HG) is often associated with gestational transient thyrotoxicosis (GTT) due to elevated human chorionic gonadotropin (hCG) levels, affecting approximately 60% of HG patients. GTT is generally self-limiting, resolving by the first or early second trimester without requiring pharmacological treatment. We present the case of a 38-year-old pregnant woman, in her third pregnancy, who experienced severe nausea and vomiting at 6 weeks of gestation, with a Pregnancy-Unique Quantification of Emesis/Nausea (PUQE) score of 12. Laboratory findings indicated low thyroid-stimulating hormone (TSH) and high free thyroxine (FT4), consistent with GTT, while thyroid ultrasound showed no abnormalities. The patient had a history of chronic hypertension since her first pregnancy and diabetes mellitus diagnosed a year earlier. Three weeks later, she was readmitted and diagnosed with thyrotoxic periodic paralysis (TPP) secondary to GTT. Treatment included intravenous fluids, potassium supplementation, antiemetics, vitamins, antithyroid drugs, and continued management of her diabetes and hypertension. HG, which is most common in the first trimester, is often linked to thyroid dysfunction due to hCG stimulation. While GTT is typically self-limiting, complications like TPP can arise, adding complexity to patient management, especially with coexisting conditions like diabetes and hypertension. Treatment strategies focused on symptom control, fluid rehydration, and careful adjustments of medications for thyroid, glycemic, and blood pressure management. Unfortunately, the patient did not return for follow-up, limiting further evaluation of her thyroid function in the second trimester. This case highlights the need for accurate diagnosis and timely intervention to prevent severe maternal and fetal outcomes, particularly in complex cases with multiple comorbidities.

Keywords: Hyperemesis gravidarum, hyperthyroidism, gestational transient thyrotoxicosis, thyrotoxic periodic paralysis

INTRODUCTION

Hyperemesis Gravidarum (HG) is a condition characterized by severe nausea and vomiting during pregnancy, associated with fluid and weight loss, ketonemia, ketonuria, electrolyte and acid-base imbalance, dehydration, and weight loss ≥5%.[1-3] HG typically develops between the 4th and the 10th weeks of pregnancy and resolves by the 20th week.[1] HG can lead to serious metabolic complications including malnutrition, vitamin K deficiency, Wernicke encephalopathy, acute liver and kidney failure, esophageal rupture, pneumothorax, pre-eclampsia, placental abruption, neuro-developmental delay of the fetus, preterm birth, and maternal death.[3]

HG occurred due to higher levels of pregnancy hormones, especially human chorionic gonadotropin (hCG). hCG can stimulate either the upper gastrointestinal tract or thyroid gland function activity due to its structural similarity to thyroid-stimulating hormone (TSH), potentially allowing hCG to exhibit TSH-like effects.[1,4] About 5% of women may have a serum TSH level below 0.1 mIU/L by 11 weeks of pregnancy.[5]

During pregnancy, thyroid function changes, and hormone levels shift from their normal ranges. The concentrations of total triiodothyronine (T3) and thyroxine (T4) increase, leading to gestational transient thyrotoxicosis (GTT). GTT is characterized by hyperthyroidism that develops for the first time in early pregnancy, without signs of thyroid autoimmunity or evidence of Graves' disease, and typically resolves by the end of the first trimester or early in the second trimester.[1] GTT induced by hCG can be distinguished from Graves disease by the absence of any history of thyroid disease, negative TSH receptor antibodies, and normal thyroid ultrasound findings.[5-7] Approximately 60% of patients with HG experience transient hyperthyroidism.[1] GTT is a self-limiting condition and will resolve spontaneously and rarely requires drug treatment.[2,6,8]

The primary mechanism of thyroid stimulation during pregnancy leading increased total T3 and T4 levels as a result of elevated estrogen levels, which leads to increased production of thyroid-binding globulin (TBG) and reduced T4 metabolism.[1,4,9] This mechanisms results in elevated free T4 levels. Thyrotoxic periodic paralysis (TPP) is also associated with hyperthyroidism with characterized by acute paralytic episodes and hypokalemia.[10]

CASE ILLUSTRATION

A 38-year-old pregnant woman (G3P2L2A0) presented to the emergency department with complaints of severe nausea and vomiting exceeding 10 episodes since that morning. She also reported generalized weakness, fatigue, and epigastric pain but denied diarrhea, fever, vaginal discharge, or bleeding. She did not experience palpitations, nervousness, hand tremors, heat intolerance, or anterior neck swelling. She denied blurred vision, headache, or pedal edema. Over the past year, she experienced unintentional weight loss of 7 kg. The first day of her last menstrual period was April 3, 2024. Her menarche occurred at age 15, with a history of regular monthly cycles. She had two prior full-term vaginal deliveries. Upon admission, her Pregnancy-Unique Quantification of Emesis/Nausea (PUQE) score was 12, indicating moderate HG. She had a history of diabetes mellitus managed with metformin 500 mg BID and glibenclamide 5 mg OD and hypertension diagnosed during her first pregnancy, however she does not take any drugs routinely.

On examination, the general condition was poor. Her blood pressure was 169/90 mmHg, heart rate 110 bpm, respiratory rate 22 breaths per minute, temperature 36.8°C, and oxygen saturation 98% on room air. She weighed 35 kg (pre-pregnancy weight: 34 kg) with a height of 143 cm, resulting in a BMI of 16.67 kg/m^2, categorized as underweight. Her mid-upper arm circumference was 23 cm, indicating chronic energy deficiency. There were no signs of exophthalmos or thyroid enlargement. Abdominal examination revealed epigastric tenderness. Laboratory results are

summarized in table 1 ECG showed normal sinus rhythm.

Transabdominal ultrasound confirmed a single live intrauterine pregnancy with a crown-rump length (CRL) of 0.82 cm, corresponding to 6 weeks and 3 days of gestation, with a positive fetal heartbeat. Thyroid ultrasound revealed a normal-sized gland without increased vascularity or nodules (figure 1). She was clinically diagnosed with hyperemesis gravidarum complicated by gestational transient thyrotoxicosis (GTT), diabetes mellitus, chronic hypertension, and chronic energy deficiency.

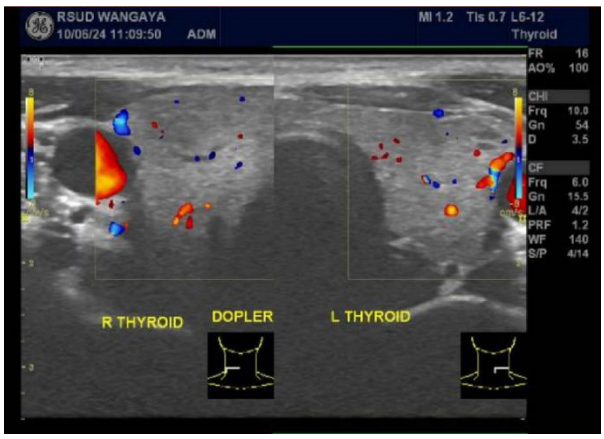

Figure 1. Thyroid ultrasound of the Patient

The patient was treated with intravenous fluids (5% dextrose and Ringer's lactate, 2000 mL/day), ranitidine 50 mg BID, ondansetron 8 mg TID, vitamin B6 10 mg OD, multivitamin infusion (B1, B6, B12), folic acid 400 mcg OD, insulin aspart 3 units TID, methyldopa 250 mg BID, and amlodipine 5 mg OD. She tolerated oral intake and was discharged after six days with a PUQE score of 7. She was prescribed ranitidine 150 mg BID, ondansetron 8 mg TID, folic acid 400 mcg OD, propylthiouracil (PTU) 100 mg OD, methyldopa 250 mg BID, amlodipine 5 mg OD, and was temporarily taken off insulin. However, she did not return for follow-up or medication monitoring.

Three weeks later, she returned with fatigue, weakness, and bilateral lower extremity paralysis (motor strength 4/5) lasting two days, accompanied by nausea and vomiting five times daily. Blood pressure was 140/90 mmHg, and heart rate 90 bpm. Ultrasound revealed a single live intrauterine pregnancy at 9 weeks 6 days (CRL 2.90 cm) with a positive fetal heartbeat. Laboratory results showed hypokalemia and elevated liver enzymes (Table 1). She was treated with intravenous potassium replacement (25 mEq potassium chloride), ranitidine 50 mg BID, ondansetron 8 mg TID, multivitamin infusion, folic acid 400 mcg OD, PTU 100 mg OD, curcuma tablets TID, and insulin aspart 6 units TID. On day three, she experienced hypoglycemia (blood glucose 50 mg/dL), prompting discontinuation of insulin.

Potassium levels normalized by day six. She was started on propranolol 10 mg BID and methyldopa 500 mg BID. Echocardiography revealed a left ventricular ejection fraction of 60%, concentric hypertrophy with mild mitral regurgitation, for which digoxin 0.25 mg BID was added. She was discharged after 21 days with improved symptoms, stabilized glucose levels, and better nutritional intake. She was discharged with the following medications: ranitidine 150 mg BID, ondansetron 8 mg TID, vitamin B6 10 mg OD, folic acid 400 mcg OD, PTU 100 mg BID, methyldopa 250 mg BID, amlodipine 5 mg OD, and potassium slow release (KSR) 1200 mg TID.

Preventing GTT can be challenging, as it is often related to the physiological changes that occur during early pregnancy. In this case, it is important to treat the precipitating factors of HG that exacerbate thyroid dysfunction, maintain adequate hydration and nutrition, and evaluate and address any preexisting thyroid disorders.

Table 1. Patient's Laboratory Results

Gestational Age	6w3d	9w6d		
Parameter			Units	Reference Values
	7th June	30th June		
Haemoglobin	15.1	12.9	g/dL	12.0 - 16.0
Haematocrit	43.4	36.4	%	37.0 - 47.0
Leucocyte	13.040	13.720	/µL	4.0 - 10.0
Platelet	297	314	10^3/µL	150 - 400
AST	27	**100**	U/L	0 - 37
ALT	**52**	**149**	U/L	0 - 42
Urea	25	15	mg/dL	10 - 50
Creatinine	0.4	0.3	mg/dL	0.3 - 1.2
Sodium	139	131	mmol/L	130 - 145
Potassium	4.3	**2.9**	mmol/L	3.5 - 5.5
Chloride	102	100	mmol/L	95 - 108
Random Blood Sugar	201	224	mg/dL	80 - 200
HbA1c	5.5	7.0	%	
TSH	**0.17**	**0.06**	mIU/L	0.35 - 5.10
fT4	**1.79**	**4.63**	ng/dL	0.5 - 1.4
Urinalysis				
Ketone	**+4**	**+4**		Negative
Glucose	**+4**	**+3**		Negative
Protein	Negative	Negative		Negative

DISCUSSION

HG incidence is more higher occurred during the first trimester, especially in multiple pregnancies compared to single pregnancy.[3] A systematic review and meta-analysis by Farshbaf-Khalili et al.[1] found a significant association between HG and thyroid function markers such as free triiodothyronine (fT3), TSH, TTG, free thyroxine (fT4), TSH, TT4, and hCG. Women with HG showed significantlyttg elevated serum levels of fT3, fT4, and TT4, while TSH levels reduced compared to women without HG, indicating a strong link between HG and GTT.[1] From Nijsten et al.[11] study findings TSH and FT4 levels are not predictive of HG severity, while Zheng et al.[12] study findings β-hCG levels correlate with the degree of HG severity and associated hyperthyroidism. Although GTT is typically self-limiting and resolves spontaneously, atypical presentations may occur, such as delayed onset, and severe symptoms requiring interventions, or prolonged duration.[13]

During pregnancy, the thyroid gland volume increases by 10-40% and occurs due to iodine deficiency caused by active iodine transport to the fetus through the placenta, increased renal excretion, and increased iodine consumption by the maternal thyroid.[4,9] Despite the elevation in total thyroid hormone levels, the free-form remains steady, maintaining a euthyroid state in pregnant woman.[9] Reference ranges for thyroid function tests during pregnancy is different due to physiological changes such as increase of TBG levels and the peak of hCG levels (see Figure 1)[14] and normal references ranges for thyroid hormones among non-pregnant and pregnancy are outlined in Table 2.

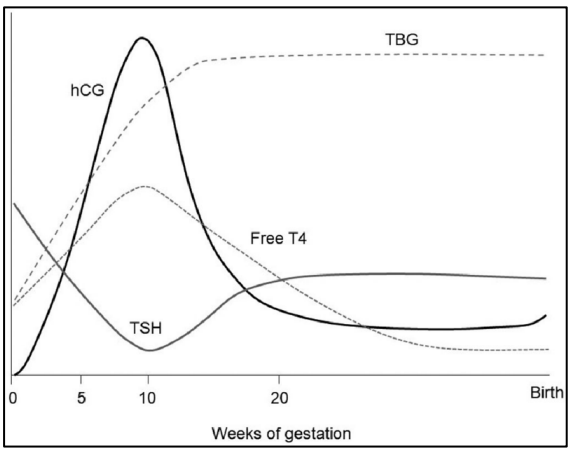

Figure 2. Alteration of thyroid function tests during pregnanc

Table 2. Normal References Range for Thyroid Hormones[4]

	Non-pregnant (fertile period)	1st trimester	2nd trimester	3rd trimester
TSH (mU/l)	0.5 - 4.1	0.6 - 3.4	0.37 - 3.6	0.38 - 4.0
Free T3 (pmol/l)	2.0 - 7.0	1.54 - 5.22	1.78 - 5.29	
Free T4	0.9 - 1.7 ng/dl	0.95 - 1.53 pmol/l	0.87 - 1.45 pmol/l	
TBG (µg/ml)	16 - 24	10 - 40	23 - 46	19 - 49

There are many overlapping symptoms of HG and hyperthyroidism such as vomiting, dehydration, and weight loss, which can also complicate preexisting with diabetes melitus. In this patient, tachycardia initially appeared to result from dehydration due to HG. However, the persistence of tachycardia post-rehydration prompted evaluation for GTT and through TSH and fT4 testing. HG complicated by GTT often presents with abnormal laboratory result such as hyponatremia, hypokalemia, mild hyperbilirubinemia, and mild-to-moderate liver enzyme elevations, which correlated with the severity of liver dysfunction.[13,15] Furthermore, GTT can also lead to severe complications, such as thyroid storm. To differentiate it, we must calculate the Burch-Wartofsky score, which in this patient was 30, indicating an impending storm. Therefore, more aggressive treatment with loading doses is required. Additionally, thyroid ultrasound was performed to ruled out with other thyroid disease and obstetric ultrasound also performed to exclude secondary causes of HG, such as gestational trophoblastic disease or multiple pregnancies.[8,16] It's essential to make an accurate diagnosis to determine the appropriate treatment, monitoring, and prognosis of the patient.

There are also reports of higher fT4-to-fT3 ratio in pregnancy involved with gestational diabetes melitus.[12] However, in this case, the patient had preexisting diabetes melitus, managed with antidiabetic medications for the past year. For HG management, the antiemetics approved for pregnancy is ondansetron with selective 5-HT3 receptor antagonist, pyridoxine (vitamin B6) 10 mg with or without doxylamine 10 mg and promethazine are recommended.[3,17] For fluid rehydration intravenous recommended for patients with HG with severe dehydration or ketonuria preferred with 10% glucose to help nutritional supplement in moderate to severe cases.[3] Given 2 liter daily of 0.9% sodium chloride solution with 20 mmol of potassium chloride intravenously over 4 h also proven effectiveness resolving of dehydration.[17] To reduce risk of refeeding syndrome and Wernicke's encephalopathy should be given thiamine (100 ml of 0.9% sodium chloride contains 100 mg).[3]

Despite thyroid dysfunction during pregnancy, universal screening is not recommended by the American Congress of Obstetrics and Gynecology (ACOG) along with the American Thyroid Association (ATA) and European Thyroid Association.[4,9] However, thyroid dysfunction should be aware because associated with fetal and maternal complications such as pregnancy loss, preterm delivery, pre-eclampsia, and increased neonatal morbidity.[4] In pregnancy, hyperthyroidism can be managed with medication antithyroid drugs namely PTU or methimazole, but PTU is commonly preferred and can be used from the first trimester.[4] The medication should be evaluated carefully because it can crosses the placenta and acts on the fetal thyroid.[4] GTT treatment must be considered initiated before 18 weeks of pregnancy due to hCG influence and possibility of normalized T4 levels in this period. In the second half trimester, the symptoms typically improve, and the medical treatment needs to be adjusted accordingly. The goal in these cases is to maintain fT4 levels at the upper normal range to minimize the dosage of anti-thyroid medication.

In this patient, the risk factors for her pre-existing diabetes remain unclear, as she has no history of gestational diabetes in previous pregnancies, no history of delivering an infant with weight ≥4000 g, and no known family history of diabetes. The management in this patient was stop oral antidiabetic medication and initiated insulin therapy as recommended that approved during pregnancy with the glycaemic targets are: (1) ≤ 95 mg/dl in the fasting state, (2) ≤ 140 mg/dl at one-hour postprandial, and (3) ≤ 120 mg/dl at two-hour postprandial glucose.[18]

The patient has a history of hypertension diagnosed prior to first pregnancy so she was diagnosed with chronic hypertension. ACOG recommended for pregnant women with severe hypertension (≥160/105-110 mmHg) should be treating with antihypertensive medications with first line nifedipine 30-120 mg/day PO or second line with methyldopa 250-3000 mg/day PO in divided doses every 6-12 hours.[19] The main goal managing chronic hypertension during pregnancy to achieve ACOG blood pressure targets with minimal medications at the lowest effective doses.[19]

Hypokalemia in this patient likely resulted from inadequate potassium intake and persistent vomiting of HG. The pathogenesis of TPP because of hyperthyroidism of serum T4 level being increased of adrenergic response made activation of NaK/ATPase channel leading to intracellular potassium shifting result of hypokalemia (Figure 3).[10,20,21] The patients also given propanolol by cardiologist to reduced the heart rate. Beta blockers can be used during pregnancy to manage the adrenergic symptoms of thyrotoxicosis like tachycardia but should be limited to short durations. They have not shown teratogenicity but can lead to neonatal bradycardia and hypoglycemia if administered late in pregnancy.[22]

Unfortunately, the patient did not return for follow-up, limiting our ability to reassess TSH and fT4 levels at the beginning of the second trimester, as hCG levels would have decreased, potentially confirming GTT resolution.

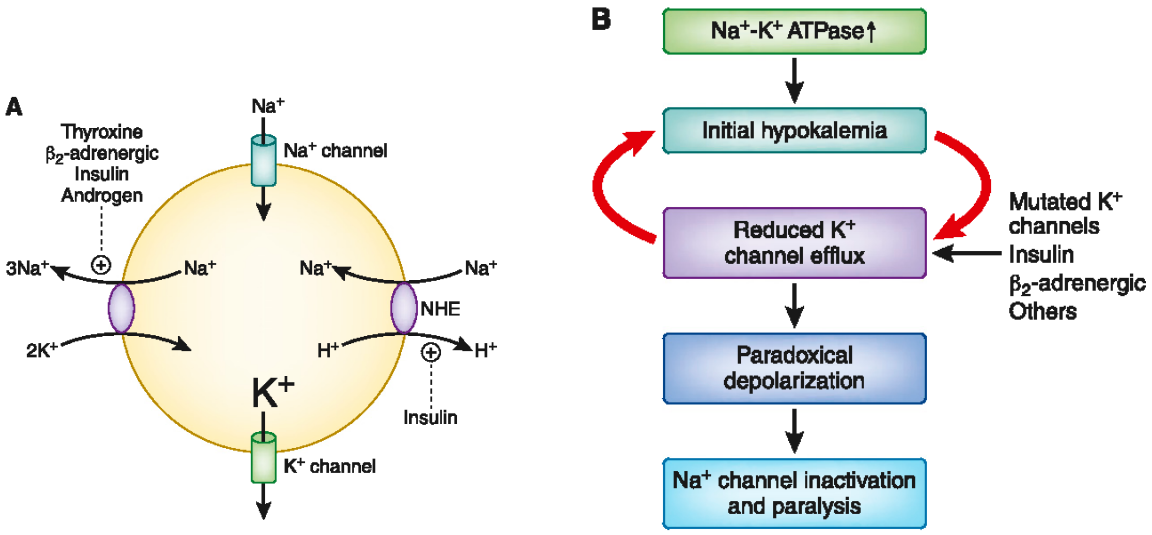

Figure 3. (A) Mechanism of TPP (B) Mechanism of hypokalemia to paralysis[21]

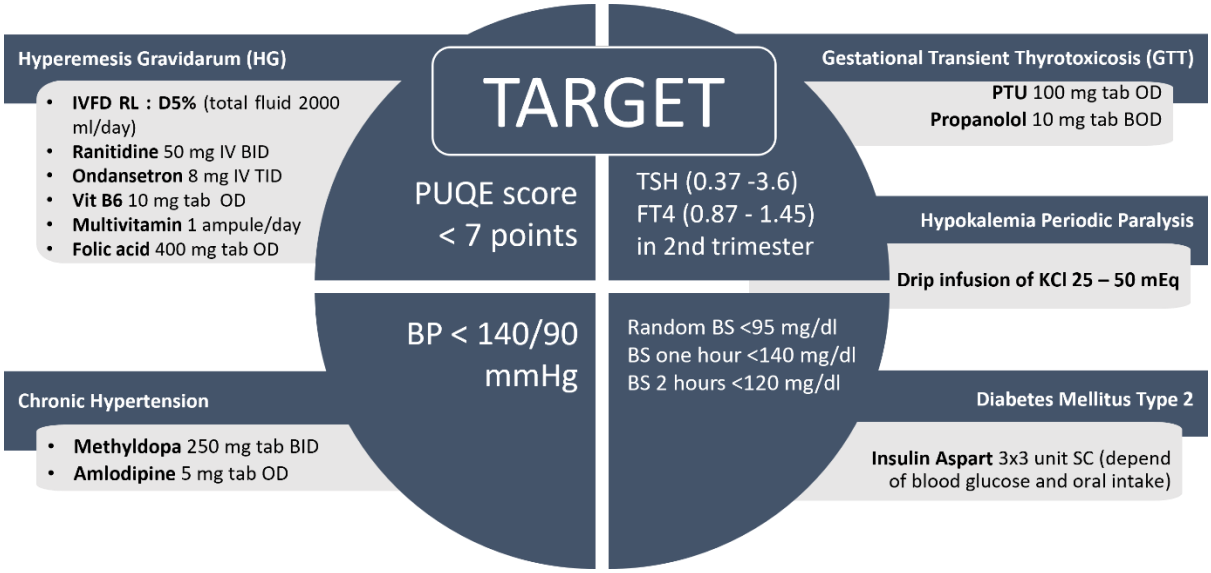

Figure 4. Patient's clinical diagnosis with the therapy given and the expected target outcome

CONCLUSION

This case highlights the importance of accurately diagnosing hyperemesis gravidarum (HG) and identifying its underlying causes, such as gestational transient thyrotoxicosis (GTT), particularly in early pregnancy. The patient presented with complications including periodic hypokalemia and elevated liver enzymes, alongside preexisting chronic hypertension and diabetes mellitus. Managing complex, coexisting conditions in the first trimester requires careful observation and a multidisciplinary approach. Early intervention and appropriate treatment are crucial to minimizing maternal and fetal complications and improving pregnancy outcomes.

REFERENCES

1. Farshbaf-Khalili A, Salehi-Pourmehr H, Najafipour F, Alamdari NM, Pourzeinali S, Ainehchi N. Is hyperemesis gravidarum associated with transient hyperthyroidism? A systematic review and meta-analysis. Taiwan J Obstet Gynecol. 2023;62(2):205-25.
2. Onyango VC, Malalu CP, Fryda WC. Transient Hyperthyroidism of Hyperemesis Gravidarum: A Case Report from Rural Kenya. Eur J Heal Sci. 2024;10(1):31-6.
3. Liu C, Zhao G, Qiao D, Wang L, He Y, Zhao M, et al. Emerging Progress in Nausea and Vomiting of Pregnancy and Hyperemesis Gravidarum: Challenges and Opportunities. Front Med. 2022;8(January):1-17.
4. Dumitrascu M, Nenciu AE, Florica S, Nenciu C, Petca A, Petca RC, et al. Hyperthyroidism management during pregnancy and lactation (Review). Exp Ther Med. 2021;22(3):1-5.
5. Morton A, Teasdale S. Physiological changes in pregnancy and their influence on the endocrine investigation. Clin Endocrinol (Oxf). 2022;96(1):3-11.
6. Springer D, Jiskra J, Limanova Z, Zima T, Potlukova E. Thyroid in pregnancy: From physiology to screening. Crit Rev Clin Lab Sci. 2017;54(2):102-16.
7. Ahmad B, Iqbal M, Ayub S, Zahir N, Afridi S. A Cross Sectional Study of Frequency of Transient Hyperthyroidism in a Tertiary Care Hospital in Patients with Hyperemesis Gravidarum. 2021;14(4):202-7.
8. Zimmerman CF, Ilstad-minnihan AB, Bruggeman BS, Bruggeman BJ, Dayton KJ, Joseph N, et al. AACE Clinical Case Reports Thyroid Storm Caused by Hyperemesis Gravidarum. AACE Clin Case Reports [Internet]. 2022;8(3):124-7.
9. Kazma JM, van den Anker J, Allegaert K, Dallmann A, Ahmadzia HK. Anatomical and physiological alterations of pregnancy. J Pharmacokinet Pharmacodyn.

2020;47(4):271-85.
10. Naik S, Talwar D, Acharya S, Kumar S, Shrivastava D. Hyperemesis Gravidarum Presenting as Severe Hypokalemic Periodic Paralysis and Type II Respiratory Failure: A Different Form of Thyroid Storm? Cureus. 2021;13(11):9-14.
11. Nijsten K, Koot MH, van der Post JAM, Bais JMJ, Ris-Stalpers C, Naaktgeboren C, et al. Thyroid-stimulating hormone and free thyroxine fail to predict the severity and clinical course of hyperemesis gravidarum: A prospective cohort study. Acta Obstet Gynecol Scand. 2021;100(8):1419-29.
12. Zheng H, Wang Q, Chen F. Correlation between Serum Beta-Human Chorionic Gonadotropin Levels and Thyroid Metabolic Function in Pregnant Women with Hyperemesis Gravidarum. Chin J Physiol. 2023;66(5):359-64.
13. Iijima S. Pitfalls in the assessment of gestational transient thyrotoxicosis. Gynecol Endocrinol [Internet]. 2020;36(8):662-7.
14. Visser WE, Peeters RP. Interpretation of thyroid function tests during pregnancy. Best Pract Res Clin Endocrinol Metab [Internet]. 2020;34(4):101431.
15. Zhou N, Zhang F, Kuriakose C, Gordon D, Parikh A. A Case of Transient Gestational Hyperthyroidism Complicated With Acute Liver Injury Successfully Treated With Plasma Exchange. Cureus. 2022;10(9):1-4.
16. Kiran HS, Rashmi N, Rajani HS, Nandish M. Gestational Transient Thyrotoxicosis Associated with Hyperemesis Gravidarum. Glob J Medical, Pharm Biomed Updat. 2021;16(3):3.
17. Jansen LAW, Shaw V, Grooten IJ, Koot MH, Dean CR, Painter RC. Diagnosis and treatment of hyperemesis gravidarum. C Can Med Assoc J. 2024;196(14):E477-85.
18. Anastasiou E, Farmakidis G, Gerede A, Goulis DG, Koukkou E, Kourtis A, et al. Clinical practice guidelines on diabetes mellitus and pregnancy: I. Pre-existing type 1 and type 2 diabetes mellitus. Hormones. 2020;19(4):593-600.
19. Battarbee AN, Sinkey RG, Harper LM, Oparil S, Tita ATN. Chronic hypertension in pregnancy. Am J Obstet Gynecol [Internet]. 2020;222(6):532-41.
20. Van den Broeck N, Poesen R, Cuypers J. Case report: thyrotoxic periodic paralysis, an unusual cause of hypokalemia. Acta Clin Belgica Int J Clin Lab Med [Internet]. 2024;00(00):1-4.
21. Lin SH, Huang CL. Mechanism of thyrotoxic periodic paralysis. J Am Soc Nephrol. 2012;23(6):985-8.
22. Ijdda S, Rafi S, Elmghari G, Ansari N. Hyperthyroidism and pregnancy. SAS J Med. 2023;10:1043-51.