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CASE REPORT

The treatment of hyperthyroidism with methimazole in a pregnant who developed agranulocytosis due to propylthiouracil

Mehmet Selim Mamiş [1], **Nida Uyar** [2], **Mehmet Ali Eren** [2], **Tevfik Sabuncu** [2]

[1] Harran University, Faculty of Medicine, Department of Internal Medicine, Sanliurfa, Turkey
[2] Harran University, Faculty of Medicine, Department of Endocrinology, Sanliurfa, Turkey

Abstract

The most common cause of hyperthyroidism during pregnancy is Graves' disease. Anti-thyroid drugs are primarily used in the treatment of pregnant women with Graves' disease. Anti-thyroid drugs' side effects include itching, jaundice, skin rash, drug fever, arthralgia, lupus-like syndrome, toxic hepatitis, vasculitis, hypergammaglobulinemia, and lymphadenopathy. Although agranulocytosis, a serious side effect of anti-thyroid drugs, is rare, it is difficult to treat when it occurs during pregnancy. In this article, we aimed to present a pregnant case with Graves' disease who developed agranulocytosis after the initiation of propylthiouracil, whose agranulocytosis was treated with granulocyte colony-stimulating factor, and subsequently, hyperthyroidism was treated with methimazole without any problem.

Keywords: Agranulocytosis, graves disease, methimazole, pregnant women, propylthiouracil

Correspondence:

Mamiş MS, Harran University Faculty of Medicine, Department of Internal Medicine, Osmanbey Campus, 63290, Sanliurfa/Turkey

e-mail: dr.mehmetselim@outlook.com

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Introduction

Overt hyperthyroidism is seen in less than 1% of pregnant women and the most common cause is Graves' disease with 0.5% (1, 2). The use of radioactive iodine is contraindicated in pregnant women (3). Due to the possible maternal and fetal risks of surgical treatment, it is recommended to perform it in the second trimester when antithyroid drugs (ATD) are contraindicated (4). Therefore, the primary treatment for Graves' disease during pregnancy includes ATD (5). Among these drugs, both propylthiouracil (PTU) and Methimazole (MMI) cross the placenta and enter the fetal circulation (6). Serious teratogenic effects can occur when MMI is used especially in the first 10 weeks (5).

Therefore, current guidelines have stated that PTU should be used in the first trimester, but MMI should be used in the next trimesters because PTU may cause fulminant liver failure (6, 7). In this article, we aimed to present the development of agranulocytosis due to PTU use, treatment of agranulocytosis with G-CSF, and the successful treatment of hyperthyroidism with MMI in a pregnant woman with Graves' disease.

Table 1: Laboratory examination at initial

Parameter	Result	Reference interval
TSH (mlU/L)	0	0.35-5.5
Free T4 (ng/dL)	2.8	0.89-1.76
Free T3 (pg/mL)	6.6	2.3-4.2
Cr (mg/dl)	0.5	0.2 – 1.11
CRP (mg/dl)	4.6	0-0.5
TRAb (IU/L)	7.59	0-1.75
ESR (mm/h)	47	<30
ALT (U/L)	13	0 – 55

Abbreviations: *ALT: alanine aminotransferase, Cr: creatinine, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, TRAb: TSH receptor antibody, TSH: thyroid stimulant hormone*

Case description

A 32-year-old female patient, who had been diagnosed with Graves' disease for about 5 years and was pregnant for 8 weeks, had been started on PTU 4 days before admission. The case presented with tremors, chills, fever, nausea, and vomiting. On physical examination, she was staring, her skin was hot and sweaty, and her tonsils were cryptic. Her body temperature was 39.8 ^{o}C, pulse 115/min, and arterial blood pressure was 110/70 mmHg. In the complete blood count, the leukocyte count was 1260/µL, the neutrophil count was 424/µL, the platelet count was 151x10^{3}/µL, the hemoglobin value was 8.29 g/dL, and the hematocrit level was 26.2%. Other laboratory values are shown in Table 1.

The patient was hospitalized with a diagnosis of agranulocytosis and neutropenic fever due to PTU use. PTU treatment was terminated and empirical antibiotherapy was started. In addition, granulocyte colony-stimulating factor (G-CSF) was administered subcutaneously at 30 MU/day for 5 consecutive days. On the third day of treatment, her body temperature decreased to normal and her leukocyte and neutrophil values returned to normal (Table 2). Propranolol and cholestyramine treatment was started in the patient whose hyperthyroidism still continued. The patient, who was planning to have a total thyroidectomy in the second trimester, was discharged with her current treatment.

The patient who had a TSH value of 0.01 mlU/mL, fT4 value of 3.41 ng/dL, and fT3 value of 9.35 pg/mL at the 16th week of pregnancy did not accept the operation. Since agranulocytosis developed with PTU before, MMI 2x5 mg was started for the patient. The patient was followed up at three-week intervals, and the MMI dose was adjusted according to the hormonal levels. There was no decrease in leukocyte values during follow-up. TSH value of the patient was measured as 0.01 mlU/L, fT4 as 1.36 ng/dL, fT3 as 4.0 pg/mL in the patient, who used MMI as 1x2.5 mg at the 34th week of the pregnancy, and the same dose of medication was continued. A healthy live birth was achieved by cesarean in the 40th week of pregnancy.

Discussion

Overt hyperthyroidism in pregnant women is seen as less than 1% and the most common cause is Graves' disease (1, 2). If hyperthyroidism is not treated in pregnant patients, complications such as spontaneous abortion, preterm birth, low birth weight, preeclampsia, and heart failure that increase fetal and maternal mortality risk can be seen (8). Radioactive iodine is contraindicated in pregnant women, and surgical treatment is applied only in the second trimester in selected cases due to its possible risks (3, 4). The primary treatment in pregnant patients with overt hyperthyroidism due to Graves' disease is ATD (5). The most commonly used thionamide group ATD are PTU and MMI. Common side effects of ATD are minor, and they include itching, skin rash, drug fever, arthralgia, and lymphadenopathy. More rarely, several major side effects such as jaundice, lupus-like syndrome, hypergammaglobulinemia, toxic hepatitis, cholestatic jaundice, and vasculitis may develop with these agents.

Agranulocytosis due to ATD, which occurs with a significant decrease in the neutrophil count (often less than 500/mm^{3}) and the presence of fever and/or signs of infection, is rarely seen (0.2 - 0.5%), but if not diagnosed and treated quickly, it can cause serious consequences, including death (9). Agranulocytosis risk is higher within the first 3 months of treatment, and its

Table 2: Course of blood counts during G-CSF treatment

	First day	2. day	3. day	4. day	5. day	7. day	Reference interval
Leucocyte ($x10^3/mm^3$)	1.88	1.37	1.54	1.94	2.59	5.64	3.7-10
Neutrophil ($x10^3/mm^3$)	0.41	0.15	0.17	0.24	0.75	2.56	1.63-6.96
Hemoglobin (gr/dl)	8.8	9.2	8.8	9.1	8.8	10.2	12-18
Platelet ($x10^3/mm^3$)	168	180	133	148	133	165	142-424

occurrence is independent of the dose (10). Thus, routine blood count monitoring is not recommended to prevent agranulocytosis related to ATD use. When sore throat and fever occur, the patient should be advised to discontinue the drug and consult the doctor (9, 10). In our case, agranulocytosis also occurred within the first days. Advanced age, neutrophil count less than $100/mm^3$, and sepsis development are poor prognostic factors in agranulocytosis caused by ATD (11). There were no bad prognostic factors in our case.

It has been shown that the use of G-CSF in cases with agranulocytosis shortens the time to recovery of the granulocyte count, and reduces infection-related complications and mortality (12). The mean recovery time of granulocyte count with the use of G-CSF has been reported as 6-8 days (12). In our case, the neutrophil count improved on the 7th day of G-CSF treatment. It has been found that the use of G-CSF during pregnancy is well tolerated, safe, and does not cause any serious side effects (13, 14). We did not observe any side effects related to the use of G-CSF in the case.

The agranulocytosis of the patient improved with G-CSF treatment, but her hyperthyroidism continued. Placental transfer of thyroid hormones is limited in the first trimester and the fetus is relatively resistant to the effects of maternal hyperthyroxinemia. Therefore, maternal thyrotoxicosis occurring in the first trimester is associated with a low complication rate, while untreated thyrotoxicosis in the second and third trimesters is associated with poor fetal outcomes. The most challenging feature in terms of treatment was the pregnancy. So, it was planned to follow the patient with cholestyramine and propranolol in the first trimester and to undergo thyroidectomy in the second trimester of pregnancy. However, as the patient refused the surgery, we decided to treat her with MMI and follow her closely from the second trimester. It has been reported that cross-reactions may occur between thionamide group drugs and therefore, caution should be exercised in the use of other drugs belonging to the same group in patients who developed agranulocytosis due to this group of drugs (15, 16). In our case, agranulocytosis did not develop again with MMI.

In this case, it was found that the agranulocytosis that occurred in the pregnant patient improved rapidly with the G-CSF treatment. Furthermore, another important result of this case is that MMI can be used in the 2nd and 3rd trimesters in pregnant women who developed agranulocytosis due to PTU. To our knowledge, there are no pregnant with Graves' disease that was previously treated in a similar way in the literature.

Conclusions

It is suggested that G-CSF can be used successfully for correcting PTU-related agranulocytosis in pregnancy, MMI can be used as an alternative agent in patients who do not accept thyroidectomy, but close follow-up is required for the possible cross-reaction.

Conflict of interest:

The authors report no conflict of interest.

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Ethical approval:

Harran University's ethics committee approved the study protocol on April 1, 2021 (protocol number: E-66063783-622.99-23580) as per the ethical principles for human research specified in the Declaration of Helsinki. And also, patient consent was obtained for this case report.

Contributions

Research concept and design: **MAE, TS, NU**
Data analysis and interpretation: **MSM, MAE, NU, TS**
Collection and/or assembly of data: **MSM, NU**
Writing the article: **MAE, TS, MSM, NU**
Critical revision of the article: **MAE, TS, NU, MSM**
Final approval of the article: **MAE, TS**

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