

Thyrotoxicosis in Pregnancy Complicated by Propylthiouracil-induced Hepatitis

Lajya Devi, MD,^{1A} Rimpay Tandon, MD,^{2A}
Ibha Kumari, MD,^{2B} Anju Huria, MD,^{2C} Poonam Goel, MD^{2D}

¹Department of Obstetrics & Gynecology, Guru Gobind Singh Medical College, Faridkot, Punjab
^{1A}Associate professor, lajya.goyal@rediffmail.com.

²Department of Obstetrics & Gynecology, Government Medical College & Hospital, Sector-32, Chandigarh
^{2A}Assistant Professor, drrimpy@yahoo.com; ^{2B}Ex-Senior Lecturer, kumari.ibha@yahoo.com;
^{2C}Professor & Head, anjuhuria@yahoo.com; ^{2D}Professor, poonam1302@yahoo.com.

**Corresponding Author:* Dr. Rimpay Tandon,
Assistant Professor, Department of Obstetrics & Gynecology,
Government Medical College & Hospital, Sector-32, Chandigarh, drrimpy@yahoo.com

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Abstract. Graves' disease is the most common cause of hyperthyroidism during pregnancy. Propylthiouracil (PTU) is the treatment of choice due to its relative safety during pregnancy compared to methimazole. However, rarely, PTU causes serious complications like hepatitis. We report a case of hepatitis possibly related to PTU during pregnancy complicated by thyrotoxicosis.

Keywords • Graves' disease • Hepatitis • Methimazole • Pregnancy • Propylthiouracil • Thyrotoxicosis

Introduction

Hyperthyroidism complicates up to 0.2% of pregnancies, and Graves' disease accounts for 90%-to-95% of these cases.^[1] Medical treatment with anti-thyroid drugs is the preferred mode of therapy in such situations, as radioactive iodine is contraindicated during pregnancy.^[2]

Propylthiouracil (PTU) is the antithyroid drug often prescribed during pregnancy due to its relative safety compared to methimazole.^[3] However, rarely, PTU causes serious complications. One complication is hepatitis that leads to a management dilemma. Withdrawing the drug results in a recurrence of thyrotoxicosis that may adversely affect the pregnancy.

Case Report

A 22-year-primigravida was seen at 5 weeks of gestation with complaints of palpitation, tremors, and excessive sweating. Examination revealed diffuse thyroid enlargement and ophthalmopathy. Her pulse was 110 beats per minute and her blood pressure was 150/90 mm of Hg. Her hemoglobin was 12 gm/dL (10.5-to-14 gm/dL) and other cell lines were also with-

in their reference ranges. Baseline liver and renal function tests were within their reference ranges. Her TSH level was 0.2 U/mL (0.6-to-4.5 U/mL), her free T₃ was 6.3 pg/mL (1.2-to-4.1pg/mL), and her free T₄ was 2.96 ng/dL (0.7-to-1.72ng/dL). Thyroid ultrasonography showed that the gland was diffusely enlarged.

She was started on 50 mg of PTU and 20 mg of propranolol twice each day. Follow-up after 6 weeks revealed persistent symptoms; hence, her daily dose of PTU was increased to 300 mg. The patient finally achieved a euthyroid state with a PTU dose of 600 mg per day. Subsequent follow-ups of the patient till 32 weeks of gestation were uneventful.

At 33-weeks of gestation, jaundice was detected. Laboratory testing showed the following: a total serum bilirubin of 9.4 mg/dL (0.5-to-1.2 mg/dL), conjugated bilirubin of 7.8 mg/dL, serum aspartate aminotransferase of 302 IU/L (5-to- 40 IU/L), alanine aminotransferase of 325 IU/L (5-to-35 IU/L), alkaline phosphatase 344 IU/L (108-to-306 IU/L), and a prothrombin time index of 71% (75%-to-100%). There was no history of any preceding fever.

Viral markers for hepatitis A, B, C and E were negative and HIV serology was non-reactive. Ultrasonography of the patient's liver and gall bladder was unremarkable.

A diagnosis of PTU-induced hepatitis was made and PTU was withdrawn. The dose of propranolol was increased to 60 mg daily in three divided doses. Fetal well-being was monitored with daily non-stress testing and on alternate days a biophysical profile. Liver function tests showed improvement one week after the patient stopped the use of PTU. However, thyroid function test results showed a reversal of the hyperthyroid state: her free T₄ level was 3.5 ng/dL (0.7-to-1.72 ng/dL).

At 35-weeks of gestation, the patient complained of loss of fetal movement and features that revealed abruption. Intrauterine fetal death was confirmed with ultrasonography. Labour was induced and the patient delivered a dead fetus weighing 2.4 kg.

Two weeks after delivery, the patient developed palpitations and sweating. Her TSH was abnormally low. She was then treated with radioablation (5 mCi).

Six months after radioablative therapy, she conceived again in a euthyroid state. In the second month of pregnancy, she again developed features of Graves' disease. This time, her hyperthyroidism was controlled with 20 mg of NeoMercazole® twice daily. (NeoMercazole® is carbimazole, which is completely metabolised to methimazole, the metabolite that is responsible for the drug's clinical effects.) She tolerated the dose well and achieved euthyroid status quickly within 4 weeks. She was closely supervised till term and delivered a live and healthy baby weighing 2.6 kg at 37-weeks of gestation.

Discussion

The management of thyrotoxicosis in our patient raises important and pertinent issues. Uncontrolled thyrotoxicosis in pregnancy is associated with maternal and fetal complications. These include pre-eclampsia, thyroid crisis, preterm labour, abruptio placentae, and fetal death.^[2]

Our patient's first pregnancy was complicated with abruptio placentae and still birth. These complications were possibly related to uncontrolled thyrotoxicosis after the patient stopped the use of PTU.

The second issue of importance is whether to use PTU or methimazole to control thyrotoxicosis during pregnancy.^[4] Both drugs have been used for this purpose. PTU is preferably used in many countries

where methimazole is considered to be more often associated with fetal abnormalities like aplasia cutis, oesophageal atresia, choanal atresia, facial abnormalities, and mental retardation.^[5] However, there is now a consensus that the overall risk of congenital abnormalities from methimazole is no higher than that reported from the use of nonteratogenic drugs.^[5]

In our patient's first pregnancy, PTU was associated with hepatitis. However, methimazole produced no adverse reactions in the mother or the fetus.

The incidence of PTU-induced hepatitis ranges from 0.1%-to-0.2%.^[6] It takes the form of allergic hepatitis accompanied by laboratory evidence of hepatocellular damage.^[6] The occurrence of PTU-induced hepatitis in the third trimester of pregnancy leads to a treatment dilemma. Switching to other thionamides has been tried,^[7] but this risks potential cross-reaction and hence should be avoided.^[8]

Higher doses of PTU are associated with more adverse effects. Most often, hyperthyroidism during pregnancy is controlled with 100-to-450 mg of PTU. Occasionally, however, doses in the range of 600-to-800 mg/day are required. This is possibly related to poor compliance or altered PTU pharmacodynamics in pregnancy.

Surgery is the treatment option when persistently high doses of PTU are required or thyrotoxicosis remains uncontrolled. Surgery should preferably be performed in the second trimester.

Our case illustrates the fact that rare side effects of drugs used to control a medical condition in pregnancy may occur at any time. Hence, these patients' clinical condition should be closely monitored with liver function tests.

Our patient was interesting in one more aspect. She developed a hyperthyroid state soon after stopping PTU. Though after the delivery of the dead fetus in her first pregnancy, her hyperthyroid state was controlled with radioactive iodine. She then again developed thyrotoxicosis during her second pregnancy. This time, however, her hyperthyroidism was well controlled with methimazole and she delivered a healthy baby.

Conclusion

Hepatitis is a rare side effect of PTU, and its occurrence during pregnancy leads to a management dilemma. However, if hepatitis occurs in the second trimester, the option of surgery can be carried out. The available literature indicates that the patient can also

safely use methimazole as was seen in our patient during her second pregnancy.

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