Block and replace therapy using propylthiouracil and levothyroxine for Graves' disease during pregnancy

Sir,

A 36-year-old married lady was referred to our endocrine clinic by a general practitioner, on the background of three miscarriages (all first trimester), with difficult to control thyrotoxicosis (Graves' disease), desiring pregnancy. She had one male child aged 6 years (fit and well) and was found to have an overactive thyroid gland 9 months following the delivery of her first child. Ever since her diagnosis, she had stayed poorly controlled with an occasional under-active thyroid picture (elevated TSH), bringing out the issue of poor compliance to her antithyroid therapy. Her history included intolerance to carbimazole (skin rash) because of which oral therapy was switched to propylthiouracil (PTU). She refused other options (radio-iodine therapy and surgery) of treating the thyroid. She was a vegetarian, nonsmoker, nonethanolic without any significant family history or drug history.

Examination revealed an anxious, withdrawn lady with a pulse rate of 116 beats/min regular and fine tremors in both the hands. Her weight was 53 kg, with a body mass index of 21.5 kg/m^2. The supine blood pressure was 140/92 mm of Hg without any postural fall. She had a goiter that was smooth without a bruit or obvious evidence of retrosternal extension. She had grade 2 eye signs. Proximal muscle weakness was 4/5 in all four limbs. General and systemic examination was otherwise normal.

Biochemistry was unremarkable, except for a mild anemia (hemoglobin 10.2 gm% normocytic normochromic) and hypocalcemia (secondary to vitamin D deficiency).

She had biochemical evidence of thyrotoxicosis with free T4 2.8 ng/dl (0.9–1.7); free T3 6.5 ng/dl (1.9–3.2); TSH <0.001 mIU/ml (0.4–5); anti-thyroperoxidase antibody >1000 mIU/l (<35); anti-thyroglobulin antibody 342 mIU/l (<30); and anti-TSH receptor antibody 36.3 mIU/l (0–5.6). The technetium thyroid uptake scan revealed a diffuse thyroid uptake of 16.3% (<4%) consistent with Graves' disease. The sonography of the neck revealed an enlarged thyroid gland, but was otherwise unremarkable.

She presented to us with a dose of 150 mg/day of PTU that the general practitioner had recently increased from 100 mg/day. On reviewing previous thyroid function tests, we noticed that most of the TSH levels were suppressed with the odd value suggesting over-treatment (elevated TSH). Noncompliance versus a brittle thyroid picture was the only probability and therefore in order to achieve and maintain stability of the thyroid gland, we offered her "block and replace" oral anti-thyroid therapy, using PTU and levothyroxine. By just blocking her using PTU, we could have run the potential risk of inducing an under-active thyroid and therefore opted out, assuming the sensitive obstetric history. We initiated PTU in a blocking

dose of 400 mg/day (divided doses) and after 4 weeks were able to add a replacement dose of 50 μg/day of levothyroxine based on the FT3 and FT4 values keeping them in the upper range of normal. Within 8 weeks, her TSH was 0.6 mIU/l with high-normal FT3 and FT4 values. On her follow-up, she mentioned that she had missed her periods and might have been pregnant which we confirmed by a serum beta-HCG test. We monitored her thyroid function fortnightly for 1 month and then monthly till term while keeping a close eye on the liver function tests. The PTU dose was kept stable while the levothyroxine dose gradually increased to a maintenance dose of 150 μg/day till term. At approximately 28 weeks of gestation, we repeated the TSH-receptor antibody, 1.8 mIU/l (reduced from 36.3). She delivered a healthy baby boy who was monitored closely for any thyroid dysfunction. Immediately following delivery, we resumed her initial dose of PTU and levothyroxine and she continues to stay euthyroid while on the block and replace therapy. We plan to stop the block and replace therapy and treat her only with PTU with the aim of weaning her off it completely guided by the TSH-receptor antibody.

A thyrotoxic biochemical picture especially due to Graves' disease can be associated with both fatal maternal and fetal outcomes. It is therefore very important to have the thyroid function under reasonable control so as to avoid any obstetric fatalities. The maternal impact of uncontrolled thyrotoxicosis includes heart failure, pre-eclampsia, and gestational diabetes mellitus. Neonatal complications include preterm delivery, low birth weight, stillbirth, and mid-pregnancy neonatal mortality. Rarely TSH-receptor antibodies can induce a neonatal thyrotoxicosis. The optimal control of the thyroid gland in the mother is a matter of much debate, as it needs to be balanced against avoiding fetal and maternal mortality versus inducing hypothyroidism in the fetus. The current goal of antithyroid therapy in pregnant women with Graves' disease is to maintain fT4 levels at or slightly above the normal range. This leads to minimal fetal thyroid suppression compared to maintaining fT4 within the upper third of normal as was done earlier for it often lead to low fetal cord fT4 levels, endangering hypothyroidism in the child.[1-6] By just "block-therapy" using either PTU or carbimazole, it is often difficult to keep the fT4 in the upper range of normal if the focus is primarily on keeping the TSH in the lower range. "Block and replace therapy" provides the ideal platform for preventing fetal hypothyroidism as the fT4 can be manipulated very easily exogenously while maintaining the TSH in the low normal range in the shortest timeframe possible.

All antithyroidals seem to be reasonably effective in controlling maternal hyperthyroidism. The only question that arises is as to how safely it can be done. With recent reports of PTU-related liver failures, much concern has been expressed with its use throughout the gestational period. Previous recommendations for the use of antithyroidals included the use of PTU as the drug of first choice in thyrotoxicosis during pregnancy because of its proposed lower teratogenecity. However, current recommendations suggest the use of PTU in the first trimester unless contraindicated (intolerance: rash, agranulocytosis) and the use of methimazole as the drug of choice in the second and third trimester as it can rarely cause aplasia cutis, and choanal atresia when given in the first trimester.[7,8]

The case described here is unique because contrary to current recommendations for the use of methimazole, the option could not be exercised because of the patient's intolerance to it. The usual "block and replace" therapy involves the use of neomercazole with thyroxin. There are no documented experiences of the use of the block and replace therapy in the medical literature, especially with PTU and thyroxin, and this is the first case report describing the successful use of such a combination in a pregnant lady with Graves' disease. Although this is only a single case report, outcome studies using this therapeutic option may be useful to confirm superior maternal and fetal outcomes for pregnant ladies with Graves' disease.

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