Graves Disease in Pregnancy

Department of Family Medicine, Stamford Hospital
Katherine Mathew, MD

Introduction

Pregnancy causes significant physiological changes in a woman, one of which includes changes in thyroid hormone levels to meet the increased metabolic demands associated with pregnancy. These changes are characterized by elevated thyroxine-binding globulins (TBG) leading to increased levels of serum total thyroxine (T4) and triiodothyronine (T3). Homology between beta subunits of beta-HCG and thyroid-stimulating hormone (TSH) receptor also contributes to elevated thyroid hormone levels. Graves disease (GD) is one of the two common causes of hyperthyroidism in pregnancy. It is an autoimmune condition that occurs as a result of elevated antibodies against TSH receptor and affects about 0.2% of pregnant women. Preconception counseling in women of child-bearing age with GD is extremely important. Frequent lab testing, proper dosing of antithyroid drugs (ATD) to maintain appropriate thyroid hormone levels, the innate teratogenic effects of ATD, and close fetal monitoring are important components of prenatal care in a woman with GD.

Case

36 year old female, G1P0000, recently immigrated from Dubai, with a four-year history of Graves disease presented at 17 weeks of gestation for her initial prenatal visit. She had continued to take carbimazole 5mg once daily during the pregnancy without having received any pre or post-conception counseling. She denied palpitations, abnormal vaginal bleeding, chest pain, shortness of breath, tremors or changes to skin and hair. On physical exam, patient had normal vital signs without evidence of hypertension or tachycardia. She also did not have any evidence of exophthalmos, goiters, skin/hair textural changes or lower extremity edema.

Patient was instructed to stop carbimazole immediately and was switched to propylthiouracil (PTU) 50mg twice daily. Thyroid function tests including TSH, free T4 (FT4), total T3, and thyroid stimulating immunoglobulin (TSI), and TSH receptor autoantibodies (TRAb) were obtained. Labs were notable for markedly elevated TSI and TRAb. Additionally a relative hypothyroid state was seen as TSH was closer to the higher end of normal and FT4 was closer to the lower end of normal. The PTU dosing was subsequently decreased to 25 mg twice daily and patient was transferred to a high-risk obstetrics practice for frequent monitoring of thyroid functions tests and fetal monitoring. During the second trimester, around 19 weeks gestation, she was switched to methimazole 2.5mg once daily with gradual improvement in levels. She also underwent numerous fetal growth ultrasounds and fetal testing which were normal. Her post-dates testing at 40 weeks gestation showed oligohydramnios warranting an induction of labor. Her labor course was complicated by intrapartum gestational hypertension and arrest of descent. She underwent a primary cesarean section giving birth to a live female, 1 and 5 minute APGARS at 9 respectively without any significant complications.

Acknowledgements

Michael Marchese MD, John Morris MD, Setul Pardnani MD

Table 1: Thyroid Function Tests and Antibodies

LABS (Normal Range)	Initial labs at 7 weeks gest	2 months later at 15 weeks gest	6 months later at 31 weeks gest
TSH (0.35-4.94 uIU/mL)	3.82	2.39	1.52
Free T4 (0.7-1.5 ng/dL)	0.9	0.7	0.9
Total T3 (58-159 ng/dL)	107	176	139
TSI Ab (<0.55 IU/L)	4.68	3.95	3.66
TRAb (<1.75 IU/L)	5.16	6.12	4.97

Discussion

Management of GD can be challenging in the setting of pregnancy due to several reasons. As seen in this case, the patient was continuing carbimazole, a methimazole equivalent, throughout conception and into the first trimester of her pregnancy. ATD are known to have teratogenic effects especially during 6 to 10 weeks of gestation. Methimazole tends to have more serious effects such as aplasia cutis, omphalocele, choanal atresia, etc. Congenital malformations associated with PTU such as urinary tract malformations tend to be less severe and are surgically correctable, thus making it more amenable as a treatment option in the first trimester. In addition to the consideration of teratogenic effects of ATD, it is also important to maintain adequate levels of thyroid hormones during pregnancy.The increased metabolic demands of pregnancy require maintenance of a subclinical hyperthyroid state. Generally, thyroid levels such as total T3 and total T4 need to be maintained 1.5 times the upper limit of normal and free T4 just slightly above upper limit of normal. TSH should be closer to the lower limit or even slightly below normal for pregnancy. Caution should be taken when dosing either methimazole or PTU. Starting at lower doses will prevent hypothyroid states especially with methimazole since it is much more potent than PTU.

As seen in table 1, the patient's thyroid function tests and antibody levels were not at target ranges during the initial period. Maternal antibody levels (TSI and TRAb) three to five times the upper limit significantly increases risk of neonatal graves. Frequent measurement of antibody levels and fetal ultrasounds are warranted in the setting of elevated TRAb levels. Earliest signs of fetal thyroid dysfunction can be characterized by the presence of fetal goiter on ultrasound, heart rate > 160 bpm, intrauterine growth restriction and/or oligo/polyhydramnios.

During the postpartum period, methimazole is preferred for breastfeeding. It is also recommended to obtain repeat thyroid function tests six weeks postpartum due to higher risk of exacerbation of Graves disease in postpartum period. Labs can be repeated every six weeks if dose adjustment is needed or every four months for regular monitoring.

Conclusion

Graves disease is a condition that needs to be closely monitored during pregnancy. Preconception counseling is an imperative aspect of care that should be provided for women with GD who are of child-bearing age. The consequences of untreated GD include placental abruption, preeclampsia, intrauterine growth restriction, stillbirth, maternal heart failure and neonatal graves. The patient in this case had presented with certain concerning risks such as possible teratogenic effects that were being imposed on the fetus as she was continuing carbimazole in the first trimester and the elevated antibody levels which placed the fetus at risk for developing neonatal graves. Immediate intervention and close maternal-fetal monitoring prevented drastic complications of GD from occurring.

References

Nguyen et al. Clinical Diabetes and Endocrinology (2018) 4:4 https://doi.org/10.1186/s40842-018-0054-7

Ross, D. (2020). Hyperthyroidism during pregnancy. *UpToDate*. https://www.uptodate.com/contents/hyperthyroidism-during-pregnancy-treatment?search=hyperthyroidism%20in%20pregnancy&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1