A Resistant Grave's Disease in Pregnancy: Case Report and Review of the Literature

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Abstract

Background: Thyroid hormones are crucial regulators of early development and play an important role in the maintenance of a normal pregnancy and in the development of the fetus, particularly the fetal brain. The effective management of Grave's Disease (GD) during pregnancy is challenging for the clinician. The most common causes of hyperthyroidism are autoimmune GD and multinodular goiter.

A 35 year old lady at 28 weeks of pregnancy, a case of Graves' disease on anti-thyroid drug with uncontrolled thyrotoxic symptoms despite regular medication didn't show clinical and biochemical normalization even with the maximum dose of antithyroid drug and antihypertensive drug permissible at pregnancy. At gestational week 28, T4 and T3 remained elevated with suppressed serum TSH and high levels of TSH receptor antibody levels. The patient had to be followed up medically with guarded prognosis. On follow up patient didn't show any clinical or biochemical remission. Despite high thyroid hormones levels and higher anti-TSH receptor antibody levels all throughout the gestation and with maximum dose of PTU the patient delivered a healthy baby with no clinical symptoms of thyrotoxicosis, goitre or any stigmata of PTU in the neonate. Mother's TFT was closed monitored and anti-thyroid medication was titred. We present a rare case of resistant GD in pregnancy, in different stages of pregnancy management encountered many challenges.

Keywords: *Graves' disease, GD, Pregnancy, Propylthiouracil (PTU), Carbimazole, PIH.*

Introduction

Hyperthyroidism in women who are of childbearing age is predominantly of autoimmune origin and caused by Graves' disease, affecting 0.2% of all pregnant women. During pregnancy due to physiological changes in the maternal immune system may influence the development other autoimmune diseases. Hyperthyroidism is defined by abnormally high levels of thyroid hormone caused by an increased synthesis and secretion of thyroid hormone from the thyroid gland.(1) 26.4% population of global adult affects due to hypertension, it was remaining the leading preventable risk factor for premature death and disability worldwide. In endocrine disorders including overt and subclinical hyperthyroidism and hypothyroidism Hypertension may be the initial clinical presentation. After thyroid dysfunction correction may normalize blood pressure (BP) in most cases, therefore checking thyroid function is essential during the workup for hypertension. Careful management and control of patients suffering from hyperthyroidism are important to prevent the possible complications related to the disease itself or to the treatment.(2,3)

Case Report: A 35-year-old pregnant woman Gravida 3 para1 live 1 abortion 1 came to the emergency department with complaints of absent foetal movements since 1 dayin her 28th weeks of pregnancy was admitted to Shalinitai Meghe Hospital and Research Centre, (DMIMS) Nagpur. The patient has never experienced bleeding or trauma before. A history of previous delivery

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underwent by LSCS was with a healthy male baby in view of foetal distress followed by after 2 year (2 month) spontaneous abortion. On admission she had raised blood pressure (BP-160/100 mm of Hg) with shortness of breath. She had no prior history of hypertension, diabetics, grave`s disease. Lab investigation showed normal hemogram with renal, liver, function test, blood glucose and serum electrolytes were normal Biochemical parameters. Thyroid profile was revealed biochemically hyperthyroid state, free T4 5.49 ng/dl (0.61-1.12), free T3 31.36 pmol/L (3.8-6) and TSH 0.002 µIU/ml (0.3-5.6). She had positive anti thyroid peroxidase antibodies (2107µ/ml; Normal ≤15 µ/ml) and negative TSH receptorantibody.

She had tachycardia (pulse132/min) and a regular, high volume pulse. However, there were no postural tremors, lid retraction, exophthalmos or other features of thyroid eye disease. Pulse pressure was wide (80mm Hg),blood pressure was raised at 180/100 mm Hg; there was significant bi-pedal oedema, patient was on tablet labetolol 200mg 4 hourly, tab. Nicardia20 mg 12 hourly, tab. Phenobarbiturate 60 mg at night, propylthiouracil (PTU) 150 mg 8 hourly. USG neck diffusely enlarged thyroid gland with increased vascularity. Sonographic evaluations of the fetus had been normal at time of intialpresentation (Fetal heart rate 154/mints, gestational age corresponded to chronological age and no anomalies). Cardiac status evaluated and was within in normal limits. Every four weeks patient continued to be thyrotoxic clinically, biochemically [free T4- 4.45 ng/dl, free T3- 28.3 pmol/L, TSH- 0.001 µIU/ml]. At 30 weeks gestation patient condition remained the same and fetus sonography was normal. At 34 week gestations we repeated TRab and the antibody titer continued to be high (TRab= 33 U/L).Normal fetus, placental unit and no advancement of bone age. During the follow up period patient had no symptoms or clinical signs of cardiac failure at any point of time despite being frank thyrotoxic. At 37 weeks gestation had underwent LSCS in view of raised BP and fetal distress, delivered female baby. No perinatal or post-natal complication was noted in baby and had normal anthropometric measurement at birth (birth weight 2.8 kg, length 50 cm and head circumference 34 cm) and no anomalies detected on clinical examination. There was no goitre, symptoms or signs of neonatal thyrotoxicosis. After 2 weeks of delivery the neonate though asymptomatic showed biochemical features of thyrotoxicosis [TSH: 0.021 mIU/ml (<20), FT4- 4.33 (1.0- 1.6ng/ml) and FT3 6.77 (2.6-4.4 pg/ml)]. The infant was monitored clinically and a repeat thyroid function test after 4 weeks showed normalization. PTU dose was titrated as required.

Discussion

The incidence of hyperthyroidism is 1 in 2000 pregnancies, with virtually all cases due to the autoimmune disease. Hyperthyroidism is hyperfunction of the thyroid gland characterized by a 15-20% increase in basal metabolism, sometimes accompanied by a mild enlargement of the thyroid gland.[4] About 90% of hyperthyroidism is caused by Grave's disease, both solitary and multiple toxic nodules and toxic adenomas. Generally Grave's disease is found that at young women that is between 20 to 40 years old and more in women than men with a ratio of 5: 1. Thyrotoxicosis is defined as excess of thyroid hormone", and this due to an increased synthesis of thyroid hormone in the thyroid gland (hyperthyroidism), but can be due to in the absence of hyperthyroidism. [5]

Pregnancy is a unique condition, in which the physiology of thyroid gland is mainly affected by 3changes, 1) due to increasedestrogen levels leads to increases levelof thyroxin binding globulin (TBG) from 12th weeks of pregnancy which reaches 2 times normallevels which will increase T4 and T3 levels in serum and change in thyroid size; 2) anincrease in the secretion of thyroid-stimulating factors(TSF) from the placenta especially human chorionicgonadotropin (HCG); and 3) pregnancy is accompanied byincrease in renal clearance of iodine and iodine loss through the photo-placental complex at the end of pregnancy leads to a decrease in iodine supply in the thyroid gland it will cause a relative iodine deficiency state. [6]

Clinical symptoms of Grave's disease are presence of tremors, non-infiltrative or infiltrative eye disorders, weight loss without knowing why, local myxedema, myopathy and onycholysis. All of these conditions never occur in a normal pregnancy. In pregnancy patients can experience hyperemesis gravidarum which can only be treated with anti-thyroid medications. An uncontrolled Graves' mother can have cardiac decompensation anytime. Infections, anemia, arrhthymias and PIH are known dreaded risk factors that can lead to cardiac failure.[7] In pregnancy, there will be immunosuppressant due to increased fetal suppressor T cell. These suppressor factors cross the placental barrier leads to supressed immune system of mother. Grave's disease often

becomes more severe in the first trimester of pregnancy, so that hyperthyroidism was diagnosed in first trimester of pregnancy. After delivery, these suppressor factors will disappear. This can explain why the exacerbation of hyperthyroidism occurs in the postpartumperiod.[8]

Antithyroid drugs that are used in the group of thioamides which work to inhibit thyroid hormonesynthesis through the blockade of the tyrosine molecule iodination process. Improvement can be seen in the first week and a new euthyroid state is reached after 4-6 weeks of treatment. The maximum permissible dose of antithyroid medication during pregnancy is 30 mg of methimazole or 40 mg of carbimazole or 600 mgof PTU. Propylthiouracil (PTU) and methimazole have been widely used in pregnant women with hyperthyroidism. In pregnancy PTU has many advantages as compared to methimazole, because PTU can inhibit the change of T4 to T3 besides inhibiting thyroid hormone synthesis and crossing the placenta less than methimazole because PTU has strong protein binds and is difficult to dissolve in water.[9] The baby was asymptomatic at birth and has elevated TSH receptor antibodies in cord blood, repeated TFT after 2 weeks of birth. At 2 weeks neonate had biochemical evidence of thyrotoxicosis with increased TSH receptor. After 2 weeks as the anti-thyroid drug clears from circulation and TSH receptor antibodies have a longer half -life (2 -3 weeks) and once the antibodies disappear the neonates achieve euthyroidism .[9,10]

Conclusion

Incidence of Grave's disease in pregnancy is not uncommon but resistant Grave's in pregnancy is very rare. Resistant Grave's disease is a difficult situation to manage and fatal complications are likely. Mother as well as neonates should frequently monitored as they are likely to have Grave's or hypothyroidism which is antibody mediated. There are difficult to manage this kind of patients due to no proper guidelines, endocrinologist find difficulty to maintain an optimal balance between maternal and fotal wellbeing.

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