Case Report

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A case of resistant Graves' in pregnancy – A clinical challenge

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Abstract

A 29-year-old lady presented at 16 weeks of gestation, a case of Graves' disease on anti-thyroid drug with uncontrolled thyrotoxic symptoms despite regular medication. Therapy with methimazole and propranolol was started at 12 weeks of gestation didn't show clinical and biochemical normalization even with the maximum dose of antithyroid drug permissible at pregnancy. At gestational week 20, T4 and T3 remained elevated with suppressed serum TSH and high levels of TSH receptor antibody levels (TRAb =39.5 U/L, Normal value <1.7U/L). Anomaly scan at 20 weeks showed normal fetal study. Definite management of surgery was considered at second trimester in view of resistant Graves' disease not responding to medical therapy. As the patient and her family refused surgical procedure, the patient had to be followed up medically with guarded prognosis. Subsequently on follow up patient didn't show any clinical or biochemical remission. TSH receptor antibody levels estimated at 34 weeks also showed higher values (38U/L). Fetal well-being was monitored on a regular basis. Despite high thyroid hormones levels and higher anti-TSH receptor antibody levels all throughout the gestation and with maximum dose of methimazole the patient delivered a healthy baby with no clinical symptoms of thyrotoxicosis, goitre or any stigmata of methimazole fetopathy in the neonate. Mother's TFT was closely monitored and anti-thyroid medication was titrated. Here we present a rare case of resistant Graves' in pregnancy where we encountered many challenges to manage the case at different stages.

Keywords: Graves' disease, Pregnancy.

INTRODUCTION

Graves' disease is an autoimmune disorder that occurs in women of reproductive age groups. The pathogenesis is autoimmunity against the TSH receptor ^[1], which in turn produces antibodies that stimulate the TSH receptor leading to hyperthyroidism. Graves' disease in pregnancy normally has a course characterised by exacerbation in first trimester followed by a phase of relapse/ well controlled thyrotoxicosis in last trimester (due to immunosuppression) and further remission may occur during post-partum period. The effects on fetus and neonate born to Graves' mothers depend on the duration of illness and the levels of TSH receptor antibodies at 24-28 weeks ^[2]. Here we present a rare case of a lady with resistant Graves' disease throughout her pregnancy despite being on maximum dose of antithyroid medication (with TSH receptor antibody more than 15 times the normal value) which is a unusual course of Graves' in pregnancy making it a rare presentation. We would also like to discuss the difficulties that we encountered in managing this case at different stages of pregnancy. So far to our knowledge no such case has been reported.

CASE REPORT

A 29 year-old woman Gravida 2 para 1 with no living issue presented with progressive symptoms of tremors of hands, palpitation, heat intolerance, protrusion of both eye balls and neck swelling since 2 years. She sought medical attention due to amenorrhea for 3 months where she was found to be pregnant (12 weeks gestation) and also diagnosed to have Graves' disease. She was started on tab. methimazole 30 mg with tab. propranolol 40 mg per day. Despite taking regular medications for 6 weeks her symptoms persisted and her biochemical parameters were in frank thyrotoxic level and hence referred to our centre. She had no history suggestive of malabsorption. She also had a history of IUD at 28 week gestation 2 years ago for which details were not available. No history of gestational diabetes mellitus or pregnancy induced hypertension during previous pregnancy or any gross anomaly noted in the IUD fetus. On admission to us (at 16 week gestation) she had signs of thyrotoxic features and had a diffuse goitre with bruit heard over both upper pole of the glands and with no signs of infiltrative ophthalmopathy (clinical activity score of

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0/7 bilaterally) or dermopathy and no signs of cardiac failure. Other system examination was within normal limits. Lab investigation showed normal hemogram with serum T4 340 nmol/L (58.1-154.8), T3 5.8 nmol/L (1.2-3.1) and TSH <0.01 mIU/L (0.4-4). Renal function, liver function test, blood glucose and serum electrolytes were normal. USG neck diffusely enlarged thyroid gland with increased vascularity. Sonographic evaluations of the foetus had been normal at time of initial presentation (Fetal heart rate 154 /min, gestational age corresponded to chronological age and no anomalies). Cardiac status evaluated and was within normal limits. In view of her ongoing thyrotoxic status (clinically and biochemically) the dose of tab.methimazole was stepped up to 40 mg daily. Four weeks later (at 20 weeks of gestation) patient continued to be thyrotoxic clinically and biochemically with high levels of TRAb [TSH : 0.005, serum T4 300 nmol/L (58.1-154.8), T3 5.6 nmol/L (1.2-3.1) and TRAb was high at 39.5 U/I]. Anomaly scan was done at 20 week and was normal [Fetal heart rate: 158/min, gestational age corresponded to chronological age, normal placenta with normal cranium, digits, heart, kidney, neck, stomach, long bones and biophysical profile]. Despite being complaint on 40 mg methimazole for more than 8 weeks and patient continuing to be frank thyrotoxicosis we advised the need of thyroidectomy after adequate preparation. But patient family refused to undergo the surgical procedure and wanted to continue medical therapy despite explaining the prognosis. Four weeks later (at 24 weeks gestation) the patient continued to be thyrotoxic clinically and biochemically (TSH: 0.007, T4 296 nmol/L (58.1-154.8), T3 5.2 nmol/L (1.2-3.1) and 75 gram OGTT: Normal) and fetal sonography done at this time showed no abnormalities. Medications continued in same dose with frequent monitoring of fetus and mother. 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). Fetal sonography done at this time too showed 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 38 weeks gestation patient had a spontaneous labour and delivered a baby girl per vaginam. No peri-natal or post-natal complication was noted. Baby 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, vault defects or stigmata of methimazole embryopathy. Cord blood sample were sent for TFT and TRAb antibody. The neonate at birth had a normal TFT with high TSH receptor antibody (TSH receptor : 16.1 IU/L). 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. Methimazole dose in the mother was titrated as required.

DISCUSSION

The prevalence of Graves' disease in pregnancy is 0.2% and among these Graves's mothers the prevalence to have a neonate with hyperthyroidism ranges from 1/4000 to 1/50,000 [3]. Graves' disease in pregnancy has a predictable course. In the initial trimester there is a phase of exacerbation of thyrotoxicosis followed by phase of controlled thyrotoxic phase / relapse during the second and third trimester. The phase of controlled/ relapse during the later trimesters are attributed to the immunosuppressive role played by the placenta which tend to decrease the TSH receptor antibody levels in the mother [4]. In rare occasions this norm may not follow turning the clinical course difficult to manage. In our case the patient had a history of thyrotoxicosis for 2 years and an unexplained fetal demise previously. She had never received treatment prior and had a fairly large goitre at presentation. The maximum permissible dose of antithyroid medication during pregnancy is 30 mg of methimazole or 40 mg of carbimazole or 600 mg

of PTU [5]. Despite patient being on 30 mg methimazole for more than 8 weeks, being compliant to medication (all doses were given under medical supervision in our ward) and no history of gastro-intestinal malabsorption we had to step up our dose to a little higher than recommended dose in pregnancy (to 40 mg per day). But patient continued to be thyrotoxic all through her pregnancy. Also her TSH receptor antibodies were high at 20 weeks and 34 weeks respectively (more than 3 times the upper limit of normal). It should be understood that untreated Grave's presenting with large goitre and TSH receptor antibody more than 3 times the upper limit of normal range predicts the possibility of uncontrolled thyrotoxicosis in pregnancy [5]. Uncontrolled thyrotoxicosis posed a clinical challenge and we searched for an alternative medication that can be given in pregnancy to control thyrotoxicosis. Drugs like potassium iodide, cholestyramine and perchlorates are been suggested by few authors, but their efficacy and safety in pregnancy has not been ascertained and hence to use these medications during pregnancy had no concrete basis [5]. We didn't switch to PTU as there was no specific advantage to chose PTU over methimazole in resistant Graves' disease.

We considered total thyroidectomy at second trimester to render the mother euthyroid and gave the family the option. But the patient family refused for surgical procedure and wanted to continue medical management. With adequate counselling and explaining the future complication that could supervene due to uncontrolled Graves's disease we continued the medical management. Serial USG of fetus at monthly intervals were done and fetus had no features of hyperthyroidism, hypothyroidism or any anomalies. Also to mention at this point is, if the patient's family did give consent for surgical procedure it would have been a difficult task and the complications that could rise intra and post operatively [6]. We clinically anticipated the high likelihood of having a fetus or neonate with hyperthyroidism as mother had risk factors for the same. The risk factors of having an increased chance of fetal or neonatal hyperthyroidism are enumerated below [3] :

- a, Three times normal TSH receptor antibodies (best predictor of fetal/neonatal thyrotoxicosis)
- b, Clinical thyrotoxicosis in 3rd trimester or history of thioamides in 3rd trimester
- c, Family history of TSH receptor mutation
- d, Features of fetal hyperthyroidism in the fetus

An uncontrolled Graves' mother can have cardiac decompensation anytime. Infections, anemia, arrhythmias and PIH are known dreaded risk factors that can lead to cardiac failure. Fortunately throughout the pregnancy there was no such complication in mother or fetus. At term without any perinatal complication a healthy baby was born. The baby had no features of neonatal hyperthyroidism or hypothyroidism. Cord blood TFT was estimated and within normal limit. TSH receptor from cord blood showed elevated antibodies (16 IU/L, more than 3 times its upper limit of normal). Since the baby was asymptomatic at birth and has elevated TSH receptor antibodies in cord blood we repeated TFT after 2 weeks of birth. At 2 weeks neonate had biochemical evidence of thyrotoxicosis with increased TSH receptor. It has been seen that about 3 % of neonates born to Graves' mother has biochemical thyrotoxicosis without any symptoms. This phase is attributed by the antithyroid drug that reached the fetal compartment from the mother during pregnancy and protects the fetus from developing fetal or neonatal hyperthyroidism. But at end of 2 week as the antithyroid drugs clears from the neonatal circulation, hyperthyroidism may become evident biochemically and later clinically [3]. TSH receptor antibodies have a longer half life (2 -3 weeks) and once the antibodies disappear the neonates achieve euthyroidism [5]. In view of this we decided to defer treatment for the infant but followed by the baby closely.

CONCLUSION

Graves' in pregnancy is not uncommon but resistant Grave's in pregnancy is rare. Resistant Graves' disease is a difficult situation to manage and fatal complications are likely. Neonates born to such mother should be frequently monitored as they are likely to have Graves's or hypothyroidism which is antibody mediated. There are no definitive guidelines given to manage this group of patients and an area where endocrinologist find difficulty to strike an optimal balance between maternal and fetal well being.

Conflicts of interest: The authors declare that there is no conflict of interest.

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