Review Article

Fetal and neonatal thyrotoxicosis

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ABSTRACT

Fetal thyrotoxicosis is a rare disease occurring in 1 out of 70 pregnancies with Grave's disease or in 1 out of 4000-50,000 deliveries. The mortality is 12-20%, usually from heart failure, but other complications are tracheal compression, infections and thrombocytopenia. It results from transfer of thyroid stimulating immunoglobulins from mother to fetus through the placenta. This transplacental transfer begins around 20th week of pregnancy and reaches its maximum by 30th week. These autoantibodies bind to the fetal thyroid stimulating hormone (TSH) receptors and increase the secretion of the thyroid hormones. The mother has an active autoimmune thyroid disease or has been treated for it in the past. She may be absolutely euthyroid due to past treatment by drugs, surgery or radioiodine ablation, but still have active TSH receptor stimulating autoantibodies, which can cause fetal thyrotoxicosis. The other features of this disease are fetal tachycardia, fetal goiter and history of spontaneous abortions and findings of goiter, ascites, craniosyntosis, fetal growth retardation, maceration and hydrops at fetal autopsy. If untreated, this disease can result in intrauterine death. The treatment for this disease consists of giving carbimazole to the mother, which is transferred through the placenta to the fetus. The dose of carbimazole is titrated with the fetal heart rate. If the mother becomes hypothyroid due to carbimazole, thyroxine is added taking advantage of the fact that very little of thyroxine is transferred across the placenta. Neonatal thyrotoxicosis patients are very sick and require emergency treatment. The goal of the treatment is to normalize thyroid functions as quickly as possible, to avoid iatrogenic hypothyroidism while providing management and supportive therapy for the infant's specific signs and symptoms.

Key words: Antibodies, fetal thyrotoxicosis, thyroid-stimulating, transplacental

Introduction

Fetal and neonatal thyrotoxicosis are names given to the same disease manifesting at different periods of life. When it manifests in utero it is called fetal and when it manifests after the baby is born it is called neonatal thyrotoxicosis. Usually, fetal thyrotoxicosis continues as neonatal thyrotoxicosis after birth. The prevalence of Grave's disease in pregnancy is 0.2%. Of those pregnant patients with Grave's disease 1-12.5% result in neonatal thyrotoxicosis. A further 3% have biochemical thyrotoxicosis in the absence of symptoms.[1] Thus, the prevalence of neonatal thyrotoxicosis is 1/4000-1/50000 pregnancies.[1] In patients who require treatment for Grave's disease in the last trimester of pregnancy the prevalence of neonatal thyrotoxicosis is as high as 22%.[1] The mortality is 12-20% due to heart failure, but other complications are tracheal compression, infections, thrombocytopenia.[1] Thus neonatal thyrotoxicosis is uncommon, but not a rare disease which can be fatal.

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Etiopathogenesis

Grave's disease is an autoantibody mediated autoimmune disease characterized by thyrotoxicosis. This disease is caused by thyroid stimulating hormone (TSH) receptor stimulating antibodies (TSHR).[2]

During pregnancy in Grave's disease, patient's thyroid stimulating antibodies can cross the placenta like all immunoglobulin G (IgG) antibodies and stimulate the fetal thyroid triggering fetal thyrotoxicosis, which lasts until the maternal antibodies disappear from the fetal circulation.[3-5] The prevalence of fetal thyrotoxicosis is low because pregnancy is a state of generalized immunosuppression[2]

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and levels of thyroid receptor antibodies (TRAb) are reduced in pregnancy[6] and only women who have three to five times normal levels of thyroid stimulating immunoglobulins (TSIs) result in fetal and neonatal thyrotoxicosis.[2]

Although transplacental passage of maternal antibodies (IgG class) to the fetus does occur early in gestation, the fetal concentration is low until the end of second trimester. Placental permeability then increases such that in the last trimester, fetal levels are equivalent to maternal. This change in permeability as well as ability of the fetal thyroid to respond to TSH and TRAb explains why fetal hyperthyroidism occurs in the second half of pregnancy.[7]

Even women of Grave's disease who are euthyroid due to anti-thyroid medication or hypothyroid due to thyroidectomy or radioiodine therapy can have high levels of TRAb in their sera, which can cause fetal or neonatal thyrotoxicosis. Patients who have had radioiodine ablation are known to have persistent antibody levels.[8-10]

The guidelines of the American thyroid association (ATA) for the diagnosis and management of thyroid disease during pregnancy and postpartum published in 2011 recommend measurement of TRAb during 24-28 weeks of pregnancy and if the value is over three times normal, close follow for fetal thyrotoxicosis is recommended.[2]

Most TRAb can be divided into two categories. First are assays that detect TRAb in patient's sera by their ability to compete for binding of TSH receptor with a known TSH receptor ligand, which is TSH or TSH receptor antibody. These assays cannot differentiate between stimulating and non-stimulating TRAb. Second are assays that detect cAMP production in cells incubated with patients sera. These assays identify only stimulating TRAb these are also called TSI assays.[2] TRAb can change from TSI to thyroid blocking antibodies and produce hypothyroidism.[2]

The other etiology of neonatal thyrotoxicosis is due to activating mutations in the TSH receptor and activating mutations of the stimulatory G prpotein in Mcune Albright syndrome.[1] This is autosomal dominant in inheritance. This entity should be suspected if there are more than two generations affected with thyrotoxicosis or there are first degree relatives with thyrotoxicosis. Inherited mutations leading to activation of the TSH receptor have been found in several pedigrees from France and other areas of the world. Some of these pedigrees had been considered as having familial Grave's disease. Activating mutations of TSH receptor result in permanent thyrotoxicosis needing definitive treatment, which is thyroidectomy.[11] A few de novo germline mutations activating the TSH receptor have been described, they also cause persistent thyrotoxicosis and need thyroidectomy.[12] Somatic mutations activating the TSH receptor have been described as the most common mechanism for hot nodules. These usually present in adults and older children but one single case of fetal onset has been reported.[13]

Clinical Picture of Fetal Thyrotoxicosis

The most important clue to the diagnosis of fetal thyrotoxicosis is the mother's history and clinical findings. The mother has active Grave's disease or has suffered from Grave's thyrotoxicosis in the past and treated with radioiodine, anti-thyroid drugs or thyroidectomy. She may be euthyroid or even hypothyroid at present. On examination either the signs of thyrotoxicosis are present or the past stigmata of Grave's in form of ophthalmopathy or scar of thyroid surgery are present. One study even described that mothers who have severe or recurrent thyrotoxicosis and those with Grave's ophthalmopathy are most likely to present with fetal or neonatal thyrotoxicosis.[14] Fetal outcome is related to control of maternal thyrotoxicosis and complications are increased in mothers who remain thyrotoxic in the third trimester. A history of previous fetal loss is an important clue.

In one case, which was treated by the author, the importance of history and physical examination is illustrated. A patient of Grave's disease treated with subtotal thyroidectomy had five pregnancies complicated with fetal thyrotoxicosis. The mother had stigmata of Grave's in the form of Grave's ophthalmopathy, goiter and the presence of clinical and biochemical thyrotoxicosis at time of presentation in the fourth and fifth pregnancy. There was documented history of three intrauterine deaths in the third trimester. The autopsy of the fetus in the first pregnancy revealed macerated still birth with autolysis of all organs. In her second pregnancy fetal tachycardia of 188 beats/min was documented and autopsy of the fetus showed goiter, pleural effusion and ascites. In the third pregnancy there was documented fetal tachycardia of 188/min and at 26 weeks gestation a macerated stillbirth. Fetal tachycardia in the fourth and the fifth pregnancies was documented by ultrasound (fetal heart rate 160-180/min). In the fourth pregnancy and the fifth pregnancy treatment of fetal thyrotoxicosis was carried out by giving the mother carbimazole, which crosses the placenta. The fourth pregnancy resulted in a live birth, but the child developed severe neonatal thyrotoxicosis, which proved fatal. The fifth pregnancy resulted in a live birth and the child is still surviving. This history and physical examination findings leave no doubt about the diagnosis of fetal thyrotoxicosis.

Fetal tachycardia is a very important clue but is not invariably present.[7] A consistent resting fetal heart rate of above 160 beats/min documented by Doppler or ultrasound is indicative of fetal thyrotoxicosis. The normal fetal heart rate is 120-160 beats/min. An important feature of fetal tachycardia due to fetal thyrotoxicosis, is a reactive non stress testing and variability in heart rate is maintained.[15] This differentiates it from the other causes of fetal tachycardia. In our country where TSI assay is not available, fetal heart rate is the most important feature.

Fetal goiter is a good clue to fetal thyrotoxicosis when present. Fetal goiter can also be present in fetal hypothyroidism due to transplacental passage of anti-thyroid drugs given to the mother. This iatrogenic fetal goiter regresses on reduction of doses of anti-thyroid drugs while that of fetal thyrotoxicosis does not. Serial ultrasonic monitoring for fetal thyrotoxicosis is an important tool.[16]

The other features of this disease are fetal tachycardia, fetal goiter and history of spontaneous abortions and findings of goiter, ascites, craniosynostosis, fetal growth retardation, maceration and hydrops at fetal autopsy. If untreated, this disease can result in intrauterine death. 5-7% off springs of mothers receiving medical or surgical treatment for thyrotoxicosis and 24% of offspring of untreated hyperthyroid mothers end in intrauterine death. Preterm delivery occurs in 4-11% of mothers treated for thyrotoxicosis during pregnancy and 53% of mothers who remain untreated. Growth retardation is due to direct effects of thyrotoxicosis and associated preeclampsia.[1]

Umbilical cord blood sampling or cordocentesis or funipunture and measurement of fetal cord blood levels is the gold standard for the diagnosis of fetal thyrotoxicosis, but carries a risk of fetal hemorrhage, bradycardia, infection and death. It should be done only if absolutely necessary and only by doctors highly experienced in doing this. This procedure should only be performed in those cases where diagnosis of fetal thyrotoxicosis is still in doubt after ultrasound.[7]

Measurement of TSH receptor antibodies i.e. thyroid receptor binding immunoglobulins and TSIs is necessary in 24-28 weeks of gestation. The ATA guidelines do not discuss the assays to be used to determine the presence of TRAb in the mother. Some believe that a screening traumatic brain injury (TBI) assay should be done and if positive followed by a TSI assay. Some believe that only a TSI assay should be performed, but this carries a risk of missing TSHR blocking antibodies. Thus, in a pregnant women who has received definitive treatment both TSI and TBI tests have a complimentary role.[2]

Fetal thyrotoxicosis is a rare disease and a high index of suspicion is needed to diagnose it. The presence of autoimmune thyroid disease in the mother active or euthyroid on treatment, fetal tachycardia or fetal goiter on ultrasonography, should alert us. TSIs are raised in 24-28 weeks. Strong correlation has been found between maternal and fetal TSI and thyrotropin binding inhibiting immunoglobulins (TBII) levels. Maternal TSI > 350-500% (n < 125%) and maternal TBII > 40-70% (n < 10-15%) before delivery have successfully predicted neonatal thyrotoxicosis.,[17] Treatment is effective in controlling fetal thyrotoxicosis and preventing fetal death.

Treatment

Once proved fetal thyrotoxicosis can be effectively treated by carbimazole or propylthiouracil (PTU) given to the mother taking advantage of the fact that both these drugs cross the placenta. Placental passage is more with carbimazole than PTU. Monitoring of the drugs is done by monitoring fetal heart rate by Doppler or ultrasound, serial ultrasound of fetal goiter size and umbilical vein sampling. Fetal heart rate is monitored weekly. The dose of carbimazole is titrated with the fetal heart rate. If the mother becomes hypothyroid due to carbimazole thyroxine is added taking advantage of the fact that very little of thyroxine is transferred across the placenta.[15]

Clinical Picture of Neonatal Thyrotoxicosis

The diagnosis of neonatal thyrotoxicosis requires a high index of suspicion. The babies at high risk for neonatal thyrotoxicosis have the following features in the mother: [1]

1. >3 times normal TSIs in 24-28 weeks of pregnancy.
2. Clinical thyrotoxicosis in third trimester or history of thionamide treatment in third trimester.
3. Family history of TSH receptor mutation and
4. Features of fetal hyperthyroidism in the fetus.

One study found that if TRAb were more than three times upper limits of normal on day 1-7 in infants who developed neonatal hyperthyroidism. Cord blood levels should be taken in cases of suspected neonatal thyrotoxicosis for free thyroxine (FT) 3, FT4/TSH and cord TRAb levels.[7]

Symptoms and signs of neonatal thyrotoxicosis can be apparent at birth or may be delayed due to the effect of transplacental passage of maternal anti-thyroid drugs or effect of coexisting blocking antibodies, but they are apparent by 10 days of life, rarely they can be delayed up to 45 days.[1]

Goiter is present in most infants. The central nervous system signs are irritability restlessness, jitteriness and restlessness. Eye signs are periorbital edema, lid retraction and exophthalmos. Cardiovascular system signs are tachycardia, arrhythmias, cardiac failure, systemic and pulmonary hypertension. Signs of hypermetabolism include voracious appetite, weight loss, diarrhea, sweating, flushing. Other signs are persisting acrocyanosis, hepatosplenomegaly, lymphadenopathy, thymic enlargement. Bruising and petechial hemorrhage are secondary to thrombocytopenia. Advanced bone age, craniosynostosis and microcephaly may be evident both in fetus and newborn.[1]

Duration of neonatal throtoxicosis secondary to maternal Grave's disease is determined by transplacentally acquired TSI and is usually 8-20 weeks, sometimes 48 weeks.[18]

Long-term Effects

Primary hypothyroidism can occur in the fetus or the mother on thionamides. Daneman and Howard[19] found craniosynostosis in six out of eight children and intellectual impairment in 4/6 children. All four children with decreased intelligence quotient had craniosynostosis. Physical growth was normal in all children whereas another long-term follow-up study by Hollingsworth and Mabry[20] reported poor growth in three of four patients and intellectual impairment in all four, but these cases had persistent thyrotoxicosis and autosomal dominant and probably were due to gene mutation in the TSH receptor.[1]

Breast Feeding

Both PTU and carbimazole are excreted in breast milk but PTU in lower concentrations. These two drugs do not affect neonatal thyroid function, there is no contraindication for both drugs, but PTU is preferred.[1]

Treatment of Neonatal Thyrotoxicosis

Neonatal thyrotoxicosis patients are very sick and require emergency treatment. The goal of the treatment is to normalize thyroid functions as quickly as possible, to avoid iatrogenic hypothyroidism while providing management and supportive therapy for the infant's specific signs and symptoms.

The treatment of neonatal thyrotoxicosis is on the same principles as that of a thyrotoxic crisis in the adult. The synthesis of thyroid hormone is blocked by carbimazole and PTU. In addition PTU blocks the peripheral de-iodination of T4-T3. The dose of carbimazole is 0.5-1.5 mg/kg/day as a single dose and that of PTU is 5-10 mg/kg/day. Lugol's iodine acts by blocking the synthesis of thyroid hormones as well as blocking the release of the hormone stored in the colloid. Lugol's iodine, which contains 5% potassium iodide is used in a dose of one drop 8 hourly. Each drop of iodine contains 8 mg of iodine.

Beta blockers, which control the adrenergic symptoms effectively as well as inhibit the peripheral iodination of T4-T3 are used in a dose of propranolol 0.27-0.75 mg/kg 8 hourly. Steroids act by inhibiting the peripheral de-iodination of T4-T3 and by compensating for hypermetabolism of endogenous steroids induced by T4 and T3. Prednisolone is used in a dose of 2 mg/kg/day. Sedatives help by alleviating restlessness and jitteriness.[1]

Supportive treatment is very important to manage respiratory distress, fluid and electrolyte imbalance, temperature and high output heart failure. Specific treatment of congestive heart failure by diuretics and digoxin may be necessary. Oxygen therapy, non-invasive and invasive ventilation may be required.

Diarrhea and hyperthermia may occur and patient may need intravenous fluids and nursing in a temperature controlled environment. Sepsis may complicate neonatal thyrotoxicosis and appropriate antibiotics may be required.

The differential diagnosis of neonatal thyrotoxicosis is sepsis, congenital heart disease, tachyarrythmias. The work-up includes complete blood count, electrocardiography, X-ray chest, blood and urine cultures, echocardiogram and renal and liver function tests. Monitoring also has to be done for side-effects of PTU and carbimazole such as leucopenia, liver dysfunction and thrombocytopenia.

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