



PEDIATRIC NEWBORN MEDICINE CLINICAL PRACTICE GUIDELINES

IDENTIFICATION AND SCREENING OF
NEONATES BORN TO MOTHERS WITH A
HISTORY OF THYROID DYSFUNCTION





	Clinical Practice Guideline
Effective Date	February 1, 2020
Approved By	Department of Pediatric Newborn Medicine Clinical Practice Council _____ CWN PPG _____ BWH SPP Steering _____ Nurse Executive Board/CNO _____

I. PURPOSE

To identify and screen infants who are at risk for the development of thyroid dysfunction due to the transference of maternal thyroid auto-antibodies. This includes primarily infants of mothers with a current or past history of Graves’ disease and those of mothers with a history of Hashimoto’s thyroiditis who required escalating doses of thyroid hormone replacement therapy throughout pregnancy.

II. BACKGROUND

Neonatal autoimmune hyperthyroidism (neonatal Graves’ disease) is a rare but serious disorder affecting approximately 2% of infants whose mothers have Graves’ disease¹. Maternal (thyrotropin stimulating hormone receptor antibodies (TRAb) can cross the placenta and can result in neonatal hyperthyroidism -or hypothyroidism. These antibodies are most prevalent in mothers with active Grave’s disease treated with an antithyroid drug, but can also be present in mothers who have been treated for Grave’s Disease in the past with subtotal thyroidectomy; or radioactive iodine.² In utero, fetuses can exhibit goiter, IUGR, oligohydramnios, tachycardia, prematurity, or death. In neonates signs of hyperthyroidism include goiter; (occasionally with tracheal compression), low birth weight, periorbital edema, hyperthermia, irritability, diarrhea, feeding difficulties, poor weight gain, tachycardia, heart failure, hypertension, hepatomegaly, splenomegaly, cholestasis, thrombocytopenia, and hyperviscosity. Maternal TRAb levels



throughout pregnancy and neonatal TRAb levels can predict infants that are at the highest risk for the development of hyperthyroidism. The risk to infants whose mother has negative TRAb levels or who themselves have negative TRAb levels is negligible.

Infants of mothers with Graves' Disease who have been on antithyroid drugs (methimazole or propylthiouracil) during the pregnancy can be born with transient hypothyroidism. Infants of these mothers should have a free T4 and a TSH on day 3 of life whether or not the TBII is positive as this is due to the maternal medication and not to maternal antibodies.

Infants of mothers on antithyroid medication become symptomatic for hyperthyroidism later than infants whose mothers are not actively being treated. Their symptoms start at 7-17 days of life and they need to have a free T4 and TSH at 10-14 days of age if their TBII is positive².

Hashimoto's thyroiditis is another form of autoimmune thyroiditis that results in thyroid follicular cell inflammation and subsequent atrophy. It is characterized by the presence of thyroperoxidase (TPO) and thyroglobulin (Tg) antibodies. There are few reports of TPO antibodies crossing the placenta; but there can also be TSH receptor antibodies (TBII) that are more likely to cross the placental barrier and affect the neonatal thyroid. The TBII in Hashimoto's thyroiditis are blocking antibodies and can result in neonatal hypothyroidism. Existence of these antibodies should be suspected if the mother with Hashimoto's thyroiditis has been requiring escalating doses of thyroid hormone replacement during the pregnancy or if she has had a previous child with congenital hypothyroidism. In mothers with history of either of these TBII should be drawn at birth and serum TSH and fT4 should be sent around 3 days of life.

There are two ways to measure antibodies that are directed against the TSH receptor in the thyroid. TRAbs and TBII synonymous and represent the measurement of all TSH receptor antibodies that that compete for the TSH receptor. These antibodies can have blocking, stimulating or neutral effect on the TSH receptor. The other method is a thyrotropin stimulating immunoglobulin (TSI) which is a bio assay and is specific for TSH receptor stimulating antibodies. TSI are sometimes measured during pregnancy. There are no commercially assays specific for blocking antibodies. A normal TBII OR a normal TSI in the second or third trimester of pregnancy usually will mean the infant is low risk if the mother has Graves' disease. But if the mother has Hashimoto's thyroiditis only a TBII would suggest that the infant is low risk as a TSI does not measure the blocking antibodies that are responsible for neonatal hypothyroidism.



III. SCOPE

The scope of these guidelines are to identify and screen neonates who are asymptomatic but at risk for the development of thyroid dysfunction. These include infants whose mothers have active or a past medical history of Graves' disease and have positive or unknown TRAb (TBII or TSI) levels. It also includes mother's who have a history of Hashimoto's thyroiditis and have required escalating doses of thyroid hormone replacement therapy during pregnancy. In mothers who have documented negative TRAbs during the pregnancy, neonates need only to be followed clinically (unless the mother has been on antithyroid drugs during the pregnancy, in which case the infant should be screened for hypothyroidism on day 3 of life).

IV. GUIDELINES

See Figure 1

Upon admission of the infant, the maternal obstetric record should be reviewed. If there is evidence of maternal thyroid dysfunction and documentation of Graves' disease, Hashimoto's thyroiditis with escalating thyroid replacement requirement, or a prior history of an infant with congenital hypothyroidism or hyperthyroidism an inquiry for maternal TBII should be pursued.

- If the mother has documented negative TBII, further evaluation of the neonate is not required (provided the neonate is asymptomatic and there is no history of antithyroid medication during the last trimester of the pregnancy). A TBII result at 20-24 weeks of gestation or later is preferred in Graves' disease but a negative TBII or TSI (at any time in the second or 3rd trimester of pregnancy would suggest that the infant is at low risk of thyroid dysfunction. In the case of suspected TRAb, mother's with Hashimoto's thyroiditis a maternal TSI is not helpful, but a negative TBII is.
- If the mother has documented positive TBII, a TBII should be drawn from the infant as soon as this is determined and ideally within 24 hours of birth.
- If there is no documentation of maternal TBII status, a TBII should be sent on the infant when this is determined.

If there is no history of maternal Grave's diseabut the mother has a history of thyroid dysfunction (on thyroid hormone replacement or antithyroid drug) inquiry about a



history of thyroidectomy or, radioactive iodine ablation should be pursued. If positive a TBII should be sent from the infant unless the thyroid dysfunction can be documented to be from a disease that is not associated with autoimmune antibodies.

- An endocrinology consultation should be obtained for any infant who has a positive TBII.

Any symptomatic infant should have serum TSH, free T4, total T3 and TBII sent as soon as possible, and an endocrinology consultation should be obtained.

In all cases of maternal thyroid dysfunction, the infant's newborn state screen (aka PKU) laboratory requisition should state "maternal thyroid disease."

Communication with infant's PCP should include the following.

- The infant's thyroid risk status should be added to the problem list and PCP report with relevant lab results and notation of any pending laboratories.
- Follow up plan should include monitoring the infant for signs/symptoms of thyroid dysfunction.
- Laboratory phone number should be provided in order to facilitate follow up of lab result by the PCP.
- If the infant's TBII is not negative by 3-5 days of age, infant should have a free T4 and TSH level drawn while results are pending. The infant should also be examined at this time. If the infant's TBII is unable to be resulted by the laboratory, the TBII should be redrawn at the 3-5 day blood draw.
- Abnormal thyroid function tests or positive TBII resulted after the infant's hospital discharge should be communicated directly to PCP office by phone. Normal lab results can be faxed to the PCP office.
- Infants with a positive TBII and any symptomatic (regardless of TBII result) infant should be managed in consultation with a pediatric endocrinologist.

GLOSSARY

Thyroid dysfunction -abnormal TSH, T4, free T4 or T3



TRAbs -Thyrotropin stimulating hormone receptor antibodies. General term for autoimmune antibodies responsible for symptoms in Graves' disease.

TBII -TSH binding inhibitory immunoglobulin (preferred test to predict risk of thyroid dysfunction in neonate, measures both stimulating and inhibiting antibodies

TSI thyrotropin stimulating immunoglobulins (slightly less accurate test, measures stimulating antibodies only) these can also be measured as part of the TBII.

TBIAB Thyrotropin Binding Inhibitory Antibody. Can rarely be present in Hashimoto's thyroiditis and cause hypothyroidism in neonates. Are present in TBII measurement.

Antithyroid drugs- PTU(propylthiouracil) or methimazole. (As methimazole can cross the placenta, it can be associated with fetal hypothyroidism). Treatment with antithyroid drugs during the pregnancy can result in a delayed onset of neonatal symptoms (7-17 days of age) when compared to onset in infants whose mothers were not treated (1-3 days of life).



REFERENCES

1. Leger, J. Management of fetal and neonatal Graves' disease; *Horm Res Paediatr.* 2017; 87:1-6.
2. van der Kaay, DCM, Wasserman, JD, Palmert, MR. Management of neonates born to mothers with Graves' disease. *Pediatrics.* 2016;137(4):e20158178
3. McKenzie JM, Zakarya M. Fetal and neonatal hyperthyroidism and hypothyroidism due to maternal TSH receptor antibodies. *Thyroid.* 2009;2(2): <https://doi.org/10.1089/thy.1992.2.155>

**Table 1:**

All symptomatic infants should have an Endocrinology consult and serum TSH, free T4, total T3 and TBII sent.

Signs of hyperthyroidism in neonates	
Goiter	Poor weight gain
Low birth weight	Tachycardia
Periorbital edema	Heart failure
Hyperthermia	Hypertension
Irritability	Hepatomegaly
Diarrhea	Splenomegaly
Feeding difficulties	Cholestasis
Thrombocytopenia	Hyperviscosity



NOTE regarding TBII laboratory

TBII is sent out to Mayo Clinic. A courier picks up for Mayo twice a day on weekdays and at approximately 2pm on weekends. The test can be drawn ahead and sent on the following day.

Results available in 24-48 hours.

NOTE REGARDING INTERPRETATION OF TSH AND TFTs IN NEWBORNS

Both TSH and free T4 are extremely variable in the first few days of life. Our lab does not report neonatal norms and most references report normal ranges in the first 5-7 days of life as being the same in spite of evidence that the values can change rapidly during this time period. It is strongly encouraged that input with pediatric endocrinology be requested to aid in interpretation of TSH and TFTs in the first week of life or in any infants of any age who have symptoms or a positive TBII.





Figure 1:

