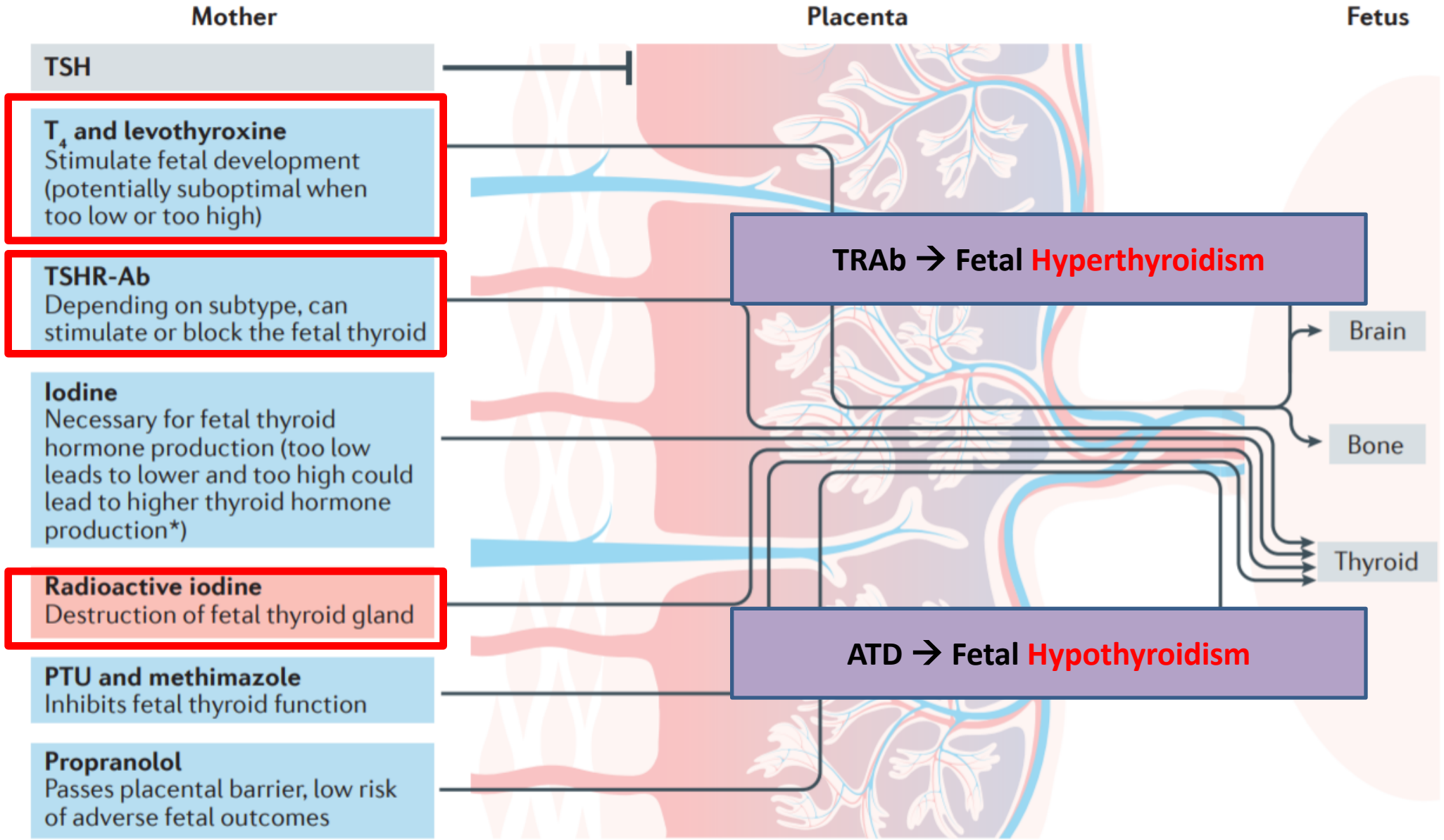
Case 1
Lessons learnt

Fetal Development of Thyroid Gland

- Fetal thyroid arises from an outpouching of the foregut at the base of the tongue (foramen cecum).
- Migrates to its normal location over the thyroid cartilage by 8-10 wk of gestation.
- Thyroid follicle cell and colloid formation is seen by 10 wk of gestation
- T4 and T3 synthesis and secretion occur from 12 wk of gestation.
- Maturation of the hypothalamic-pituitary-thyroid axis occurs over the second half of gestation.
- Normal feedback relationships are mature at 1-3 month of postnatal life.

Ari J. Wassner and Jessica R. Smith Nelson Textbook of Pediatrics, Chapter 579; Thyroid Development and Physiology, 2912-2914.e1



Korevaar TIM, Medici M, Visser TJ, Peeters RP. Thyroid disease in pregnancy: new insights in diagnosis and clinical management. Nat Rev Endocrinol. 2017 Oct;13(10):610-22

Indications for TRAb test in pregnant women with GD

- Mothers with untreated or ATD-treated hyperthyroidism in pregnancy.
- A previous history of GD with past treatment with radioiodine or total thyroidectomy.
- A previous history of delivering an infant with hyperthyroidism.
- A known history of ATD for the treatment of hyperthyroidism in pregnancy.

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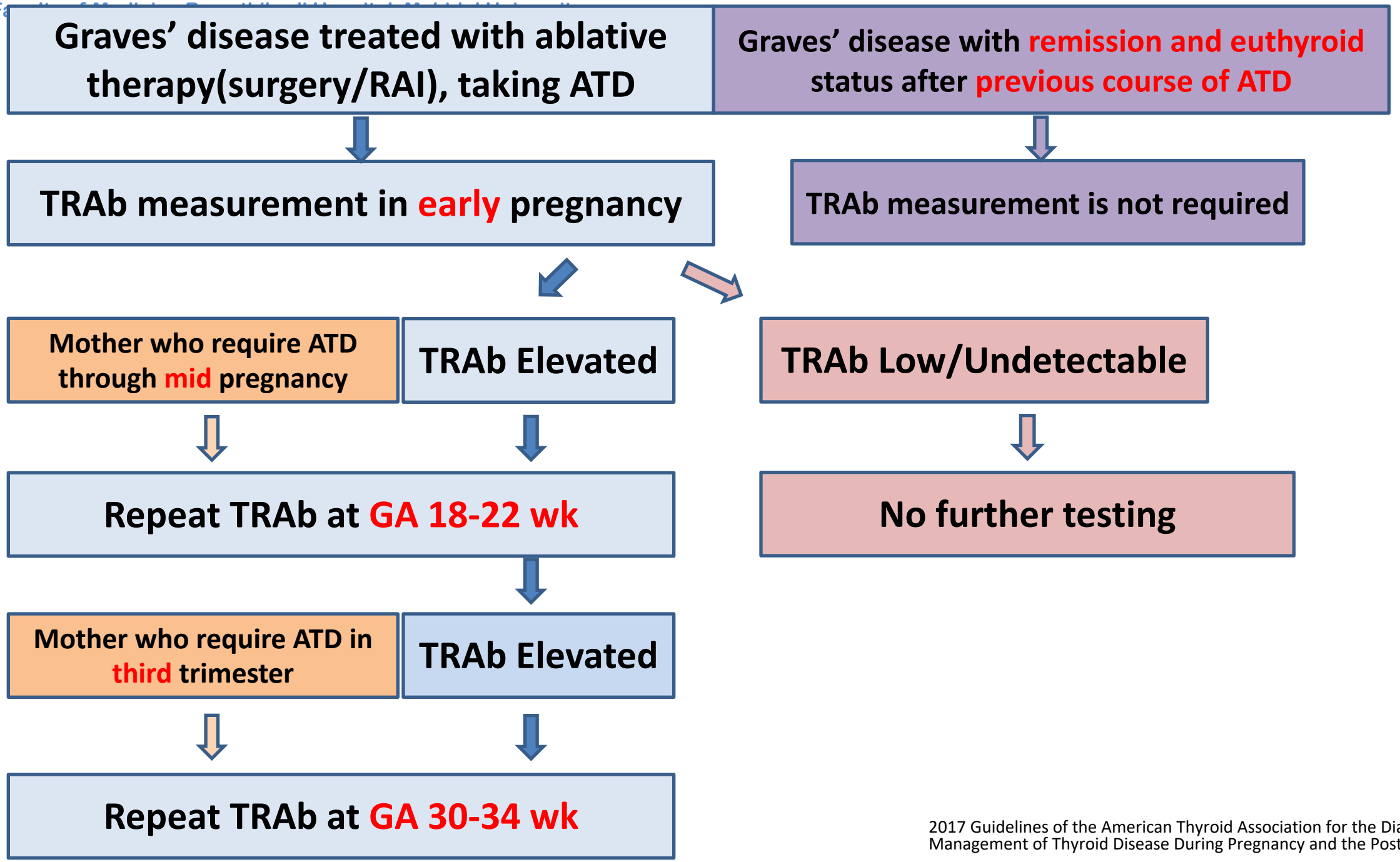

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Serial *in utero* ultrasonographic measurements of the fetal thyroid: a new complementary tool in the management of maternal hyperthyroidism in pregnancy

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- Fetal thyroid size was measured serially by transvaginal ultrasonography between 14 and 17 weeks of gestation and by abdominal ultrasonography between 18 and 37 weeks of gestation in 20 women with Grave's disease

Conclusions Serial *in utero* ultrasonography measuring fetal thyroid size in mothers with Graves' disease can serve as an effective noninvasive tool for the early detection of enlarged fetal thyroid. These findings can be used to monitor the maternal antithyroid drug dosage, thereby preventing intrauterine hypothyroidism in some cases. When a dosage reduction does not cause a decrease in fetal thyroid size, transplacental passage of thyroid-stimulating antibodies causing fetal thyrotoxicosis should be suspected.

Cohen O, Pinhas-Hamiel O, Sivan E, Dolitski M, Lipitz S, Achiron R. Serial in utero ultrasonographic measurements of the fetal thyroid: a new complementary tool in the management of maternal hyperthyroidism in pregnancy. Prenat Diagn. 2003 Sep;23(9):740-2

Figure 1—Case 1: sagittal sonogram at week 24 of gestation. Arrow marks the enlarged thyroid

Cohen O, Pinhas-Hamiel O, Sivan E, Dolitski M, Lipitz S, Achiron R. Serial in utero ultrasonographic measurements of the fetal thyroid: a new complementary tool in the management of maternal hyperthyroidism in pregnancy. Prenat Diagn. 2003 Sep;23(9):740-2

Fetal and Neonatal Hyperthyroidism

- Rare but serious disorder, occurring in only about 2% of the offspring of mothers with GD
- Major risks:
  - Cardiac insufficiency and mortality
  - Intrauterine growth retardation
  - Prematurity
  - Craniostenosis
  - Microcephaly
  - Psychomotor disabilities

Léger, J. 2016. *Management of Fetal and Neonatal Graves' Disease. Hormone Research in Paediatrics, 87(1), 1–6.*

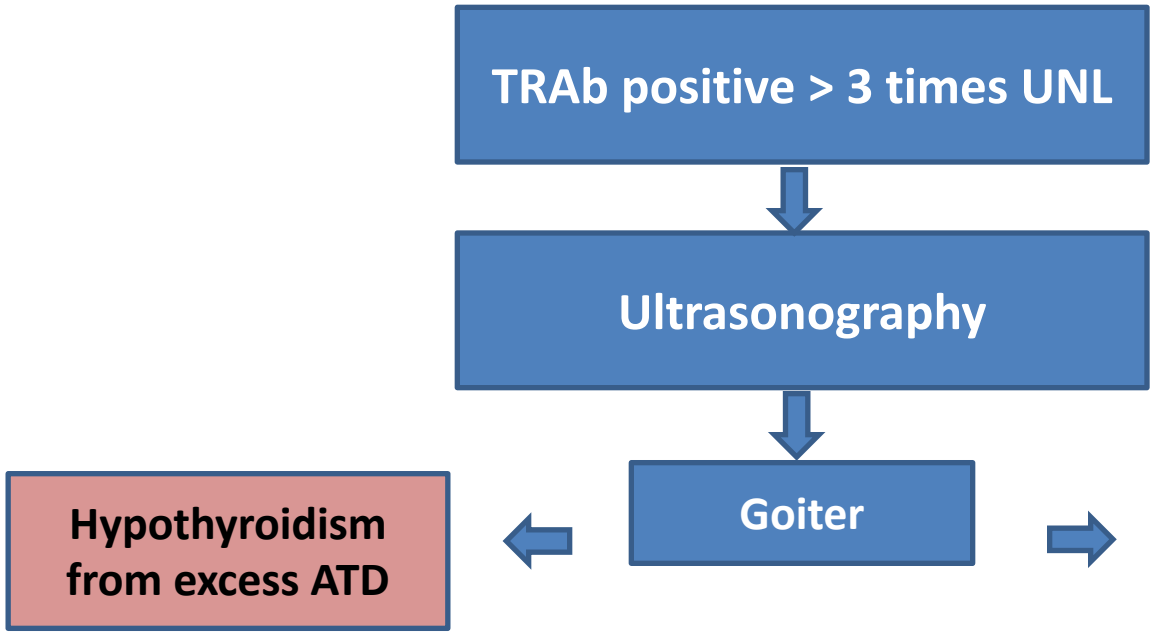
Clinical Manifestation: Fetal Hyperthyroidism

- Goiter (shown by ultrasonography)
- Tachycardia (>160 beats per minute)
- Oligohydramnios or hydrops
- Growth restriction
- Premature bone ossification

Cooper DS, Laurberg P: Hyperthyroidism in pregnancy. Lancet Diabetes Endocrinol 2013; 1:238–249

Diagnosis: During Pregnancy

- TRAb determination early in pregnancy and during the second half of gestation



Fetal hyperthyroidism should be made on clinical grounds based on maternal history, interpretation of serum TRAb levels, and fetal ultrasonography[1]
- Doppler flow of fetal thyroid gland
- Fetal bone maturation: Distal femur
- Fetal Heart rate > 160 bpm

1 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum

2 Léger, J. 2016. *Management of Fetal and Neonatal Graves' Disease. Hormone Research in Paediatrics, 87(1), 1–6.*

Umbilical Cord Sampling (Cordocentesis)

Question 61: When should umbilical blood sampling be considered in women with GD in pregnancy?

Umbilical cord blood sampling (cordocentesis) is associated with both fetal mortality and morbidity (424,425). It has been utilized when a mother is TRAb positive and treated with ATDs, a fetal goiter is present, and the thyroid status of the fetus is unclear (403,411,426). The presence of elevated TRAb alone is not an indication for cordocentesis (427).

- **RECOMMENDATION 54**

Cordocentesis should be used in rare circumstances and performed in an appropriate setting. It may occasionally be of use when fetal goiter is detected in women taking ATDs to help determine whether the fetus is hyperthyroid or hypothyroid.

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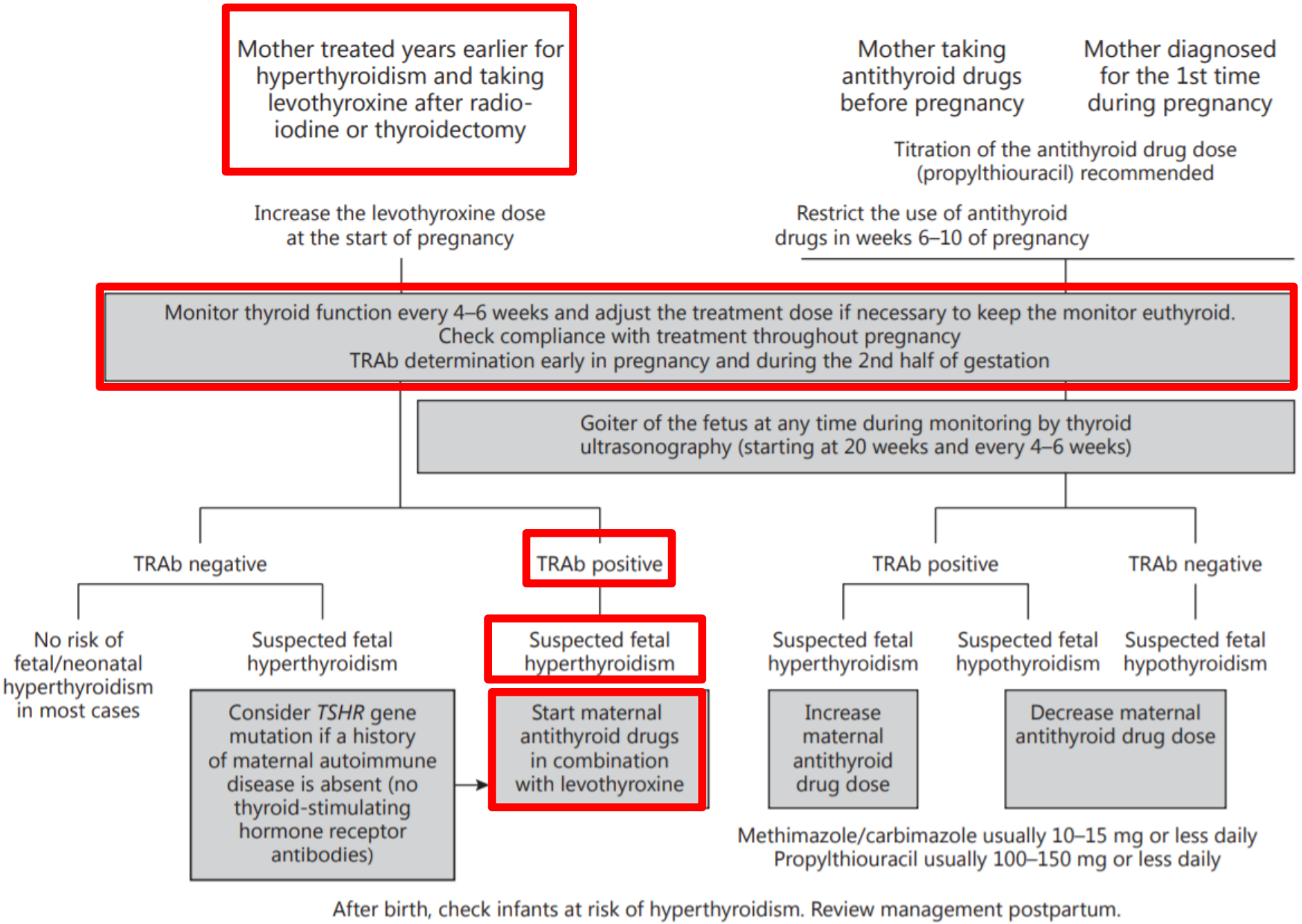
Treatment: During Gestation

- ATD treatment is commonly used to achieve euthyroidism in women with GD.
- Both MMI/CMZ and PTU are associated with an increase in the prevalence of birth defects.
- Fetal hyperthyroidism can be prevented by administering ATDs to the mother → these drugs may also expose the fetus to the risk of hypothyroidism.
- 100–150 mg PTU or 10–15 mg MMI/ CMZ daily are recommended during the second half of gestation.

Cooper DS, Laurberg P: Hyperthyroidism in pregnancy. Lancet Diabetes Endocrinol 2013; 1:238–249



Cooper DS, Laurberg P: Hyperthyroidism in pregnancy. Lancet Diabetes Endocrinol 2013; 1:238–249

Treatment: During Gestation

- Isolated fetal hyperthyroidism in a euthyroid mother can be treated with the lowest antithyroid drug dose that leads to normalisation of fetal heart rate[1]
- Maternal hypothyroidism from antithyroid drug therapy can be prevented by levothyroxine therapy[2]
- Prevent inducing fetal hypothyroidism due to excessive administration of ATD[2]

1 Cooper DS, Laurberg P. Hyperthyroidism in pregnancy. Lancet Diabetes Endocrinol. 2013;1:238–49

2 Nguyen, C. T., Sasso, E. B., Barton, L., & Mestman, J. H. (2018). *Graves' hyperthyroidism in pregnancy: a clinical review. Clinical Diabetes and Endocrinology, 4(1)*

Treatment: During Gestation

- Fetal assessment should then be performed every 1–2 weeks or as necessary[2]
  - fetal heart tones
  - assess growth
  - size of fetal thyroid gland
  - amniotic fluid index

1 Cooper DS, Laurberg P. Hyperthyroidism in pregnancy. Lancet Diabetes Endocrinol. 2013;1:238–49

2 Nguyen, C. T., Sasso, E. B., Barton, L., & Mestman, J. H. (2018). *Graves' hyperthyroidism in pregnancy: a clinical review. Clinical Diabetes and Endocrinology, 4(1)*

Treatment: During Neonatal Period

- MMI/CMZ is preferred (0.5–1 mg/kg/day, depending on the initial severity of the disease, in 3 divided doses)
- Propanolol (2 mg/kg/day, in 2 divided doses)
- The disease is transient and may last from 1–3 months, until maternal TRAbs are eliminated from the infant's bloodstream
- Mothers can breastfeed while taking ATDs (MMI/CMZ < 20 mg/day or PTU < 300 mg/day)

Cooper DS, Laurberg P: Hyperthyroidism in pregnancy. Lancet Diabetes Endocrinol 2013; 1:238–249

Outcome

- Craniosynostosis
- Transient central hypothyroidism due to thyroid regulatory system impairment
- Follow-up studies are required to evaluate the long-term neuropsychological, emotional, and behavioral functioning of children with neonatal hyperthyroidism

Cooper DS, Laurberg P: Hyperthyroidism in pregnancy. Lancet Diabetes Endocrinol 2013; 1:238–249