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Graves' Disease in Pregnancy

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Epidemiology

Graves' disease is the most common form of thyrotoxicosis in women of childbearing age. A Danish study of women in this age group has shown that:

- In the three months preceding conception the incidence of hyperthyroidism is low.
- Early in pregnancy, the number of new cases may rise, and a pre-existent hyperthyroidism may worsen, due to the stimulus to thyroid hormone synthesis by the elevated serum hCG. The excess of circulating thyroid hormones may, in turn, affect the interaction between the immune system and the thyroid, with the potential to exacerbate the underlying autoimmune condition.
- In the second half of pregnancy a significant number of women affected by Graves' disease may experience remission.
- During post-partum (up to 18 months following delivery) Graves's disease may flare up, probably due to the immunological rebound, which follows pregnancy.

Diagnosis

Normal pregnancy is associated with a series of changes, which affect interpretation of thyroid function tests (TFT):

- In the 4th week of gestation more thyroxine is converted to the hormonally inactive reverse T3 due to the deiodinase type 3, whose activity increases in the uterus and in the placenta. This is followed by an increase in circulating TSH, which maintains maternal euthyroidism.
- Starting at about the 7th week of gestation, the rising serum concentration of hCG, a structural analogue of TSH with modest agonistic receptorial activity, leads to increased thyroid output, which induces a negative feed-back on maternal TSH. This effect prevails on the increase in utero-placental deiodinase type 3 and the overall effect is a reduction in serum TSH concentration.
- Between the 7th and the 14th week, the estrogen-induced increase in circulating TBG (thyroxine-binding globulin) reduces the serum concentration of free thyroid hormones, leading to compensatory increase in TSH.

These physiological variations complicate the interpretation of TFT in pregnancy, and make it necessary to define reference values adjusted for the gestational trimester and integrated by knowledge of the assay used to measure FT4 and FT3.

Reference Values		
Age of Gestation	**TSH**	**FT4**
Week 0-6	Same as in non-pregnant women	
Week 9-12	Lower normal reference approaches 0.1 mU/L (occasionally lower between weeks 10-11)	Upper normal reference range may be about 5% higher than in non-pregnant women
2nd and 3rd Trimester	Lower normal reference same as in non-pregnant women	

Early in pregnancy, if the biochemical diagnosis of hyperthyroidism is in doubt, it is preferable to withhold treatment and monitor TFT, because subclinical thyrotoxicosis has not been associated with worsening of fetal prognosis.
The most common differential diagnosis in early pregnancy is transient gestational thyrotoxicosis, a condition more commonly observed in cases of hyperemesis or in twin pregnancies, when serum levels of hCG may be particularly elevated.

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Treatment

Untreated, clinically manifest hyperthyroidism may seriously impair maternal health and increase the risk of fetal loss.

The treatment of choice is represented by thyreostatic drugs, which, however, carry a teratogenic potential, particularly between the 6th and the 10th week.

The congenital malformations associated with the use of thyreostatics in early pregnancy have been known for years:

- **Metimazole (MMI)**: omphalocele; aplasia cutis; choanal atresia; atresia of the esophagus or other gastrointestinal segments; ocular, urinary and vascular malformations.
- **Propylthiouracile (PTU)**: head and neck malformations and urinary tract abnormalities, usually not as severe as with MMI according to the results of a Danish study.

In planning a treatment choice in fertile women with Graves' disease, the possibility of future pregnancy must be taken into account:

- Definitive treatment with radioactive iodine (RAI) or surgery prevents the risks associated with the use of medications.
- Women who opt for thyreostatic drugs may need counselling on the importance of early recognition of pregnancy through urinary testing for hCG (already positive in the 5th week).

When the pregnancy is established and there is a need for treatment in the first trimester, the medication of choice is the PTU, because the reduction in risk of congenital malformations is greater than the potential for liver damage and agranulocytosis associated with this substance.

In the event of planned pregnancy in women already on thyreostatic medications:

- If the disease is well controlled, clinically and biochemically, including serum concentration of antibodies anti-TSH receptor (TRAb), an attempt at suspending the medication may be envisaged, with the advice to measure TFT on a weekly basis during the whole first trimester.
- In the presence of factors predicting an high risk of relapse following treatment discontinuation (less than 6 months from onset of treatment; TSH < 0.01 mU/L; raised FT3; high level of TRAb; large goiter; active ophtalmopathy), the MMI must be replaced with PTU early in pregnancy, based on a 1 : 20 dosage ratio (MMI 5 mg = PTU 100 mg).

In women with mild early-pregnancy hyperthyroidism, it might be possible to consider the off-label use of alternative treatments (potassium iodide, cholestyramine, perchlorate). These substances, less commonly used in clinical practice, must however be replaced by conventional thyreostatics in the second half of the pregnancy. It is preferable that surgery, if needed, be implemented in the second trimester.

In the post-partum period, a relapse of Graves' disease in women until then in remission must be differentiated from thyrotoxicosis secondary to post-partum thyroiditis.

Potential fetal complications of maternal Graves' disease in pregnancy

Fetal Hypothyroidism: may develop after the mother has reached euthyroidism due to transplacental transfer of thyreostatics, which act on the fetal gland. The dose of these medications must be limited to the minimum amount capable to control hyperthyroidism without increasing maternal TSH above normal interval.

Isolated Fetal Hyperthyroidism: may ensue following thyroid ablation in women with persistent high serum titer of TRAb. Under these circumstances there may be a role for the «block and replace» regimen, otherwise contraindicated during pregnancy: the thyreostatic allows treatment of fetal thyrotoxicosis, while the thyroxine prevents maternal hypothyroidism. In order to recognize this situation, it is important to measure serum TRAb early in pregnancy.

Delayed Neonatal Hyperthyroidism: may develop in a newborn baby whose mother's Graves' disease has been treated with thyreostatics until delivery. This risk can be gauged by detection of levels of TRAb over three times the upper normal level in the final stages of pregnancy.

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