

ENDOCRINOLOGY IN PREGNANCY

Pregnancy and the incidence, diagnosing and therapy of Graves' disease

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Abstract

Thyroid hormones are essential developmental factors, and Graves' disease (GD) may severely complicate a pregnancy. This review describes how pregnancy changes the risk of developing GD, how early pregnancy by several mechanisms leads to considerable changes in the results of the thyroid function tests used to diagnose hyperthyroidism, and how these changes may complicate the diagnosing of GD. Standard therapy of GD in pregnancy is anti-thyroid drugs. However, new studies have shown considerable risk of birth defects if these drugs are used in specific weeks of early pregnancy, and this should be taken into consideration when planning therapy and control of women who may in the future become pregnant. Early pregnancy is a period of major focus in GD, where pregnancy should be diagnosed as soon as possible, and where important and instant change in therapy may be warranted. Such change may be an immediate stop of anti-thyroid drug therapy in patients with a low risk of rapid relapse of hyperthyroidism, or it may be an immediate shift from methimazole/carbimazole (with risk of severe birth defects) to propylthiouracil (with less risk), or maybe to other types of therapy where no risk of birth defects have been observed. In the second half of pregnancy, an important concern is that not only the mother with GD but also her foetus should have normal thyroid function.

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Thyroid hormones are essential developmental factors as first shown by Gudernatsch when he, in 1912, fed tadpoles thyroid tissue and observed metamorphosis (1). In mammals, thyroid hormones are especially of importance for brain development (2, 3), and even a few months with lack of thyroid hormones in infant

life may lead to irreversible brain damage. This is the background for the universal screening for congenital hypothyroidism performed in many countries. However, thyroid hormones are also important for normal pregnancy, and maternal thyroid disease may severely increase the risk of pregnancy complications, including

Invited author's profile

Peter Laurberg was Clinical Professor of Internal Medicine and Endocrinology, Department of Endocrinology, Aalborg University Hospital, Aalborg, Denmark. His research mainly focused on thyroid disease prevention, epidemiology, diagnosing and therapy, including studies on iodine and thyroid, and pregnancy and thyroid. He had special research interest on the risk from and optimal management of autoimmune hypo- and hyperthyroidism in pregnancy and post-partum, management of Graves' disease in general, and how the burden of thyroid disease can be minimized by adjusting the population's iodine intake. He has coauthored several international guidelines on thyroid disease management, including management of thyrotoxicosis, and thyroid disease in pregnancy. Peter Laurberg died June 20, 2016.



foetal loss (4), and compromise the future health of the child (5).

A special case is Graves' disease (GD) in pregnancy that may endanger the life of both the pregnant woman and the foetus, if not appropriately managed (6, 7). In the present review, we discuss how pregnancy alters the risk of developing GD, how pregnancy associated changes in thyroid hormone metabolism and production may hamper the diagnosing of Graves' hyperthyroidism, and how anti-thyroid drug (ATD) therapy of GD, if only focusing on the pregnant woman, may lead to severe and unforeseen foetal complications. Furthermore, we highlight how therapy of young women with GD should take into account the possibility of future pregnancy, and why very early pregnancy needs special attention in patients with GD.

Pregnancy and the incidence of Graves' disease

The incidence of thyrotoxicosis, the age distribution of the disease, and the relative contribution of various subtypes to the overall incidence of the disorder is much dependent on the iodine intake in a population (8). GD may develop at an earlier age in areas with a high iodine intake (9), but irrespective of this, GD is the common cause of thyrotoxicosis in women of reproductive age (10). The pathogenic cause of GD is autoimmunity to the TSH receptor, and hyperthyroidism from antibodies that bind to and activate this receptor (Graves' hyperthyroidism) is the signature manifestation of GD affecting $\geq 90\%$ of patients.

For unknown reason, thyroid autoimmune diseases including GD are 4–5-fold more common in women than in men (10). This gender difference is not universal among autoimmune diseases, and there is little sex difference in the incidence of type 1 diabetes (11). Moreover, ankylosing spondylitis is predominantly affecting men (11). Possibly, the mechanisms involved in the female preponderance of GD may somehow be related to the mechanisms involved in the major changes that occur in the incidence and activity of GD during and after pregnancy. Much less variation in incidence during and after pregnancy occurs in rheumatoid arthritis and inflammatory bowel disease (12).

Figure 1 illustrates the wide fluctuations in the incidence of hyperthyroidism in and around pregnancy in a Danish population study (12). The periods of high and low incidence correspond to periods where current

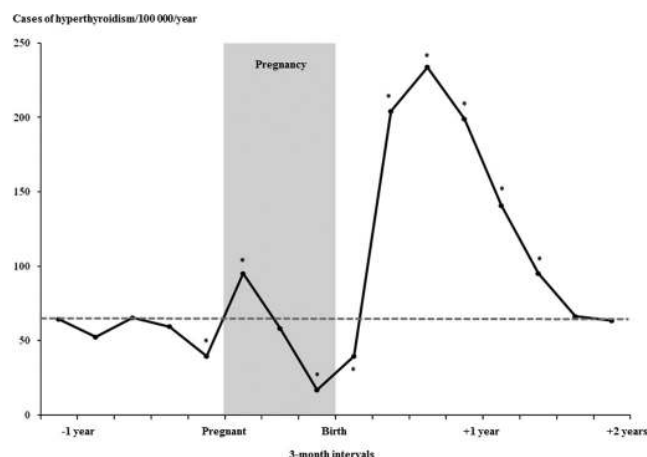


Figure 1

Incidence of hyperthyroidism before and after giving birth in 403 958 Danish women studied during 1997–2010. Only the woman's first birth in the period was included. The time periods before, during, and after pregnancy were split into 3-month intervals as indicated. The horizontal broken line indicates the overall incidence of hyperthyroidism in women over the time period (65.0/100 000/year; asterisk indicates statistical significant difference ($P < 0.05$) from this average). Reproduced with permission from Andersen SL *et al.* (12).

Graves' disease tends to worsen or enter remission. Thus, it was reported already in 1982 by Amino *et al.* from Japan (13) that pregnancy may aggravate Graves' hyperthyroidism in early pregnancy and that worsening may also occur after delivery. On the other hand, a considerable proportion of pregnant women with GD experiences remission of the disorder during the second half of pregnancy (14, 15). The late pregnancy decrease and the post-partum increase in risk of GD reflect general variation in thyroid autoimmunity, and similar changes occur in the concentrations of thyroid peroxidase and thyroglobulin autoantibodies in patients with Hashimoto thyroiditis (16) and in the incidence of hypothyroidism (17).

Considering the first trimester increase in incidence of GD (Fig. 1), such increase is not apparent in autoimmune hypothyroidism (17) and in other autoimmune diseases (12). Possibly, the early pregnancy high incidence of GD is linked to the early pregnancy thyroid stimulation by high levels of hCG, with a tendency to slight hyperthyroidism. Hyperthyroidism interacts with the immune system (18), and this may worsen the autoimmunity of GD (19). Moreover, the additive effects of high hCG and borderline GD with only subclinical and undiagnosed

hyperthyroidism may theoretically lead to overt hyperthyroidism in early pregnancy.

In addition to the high incidences of hyperthyroidism in early pregnancy and especially during the 3–18 months period after delivery, and the low incidence in late pregnancy, Fig. 1 also illustrates a relatively low incidence in the 3 month period before pregnancy. This phenomenon might be caused by a low fertility in hyperthyroid women (20), or by a deliberate postponing of pregnancy until the hyperthyroid state is amended. Because untreated hyperthyroidism may complicate pregnancy, the recommendation is to postpone pregnancy until a stable euthyroid state is reached after therapy (6, 7).

Changes in thyroid function and test reference limits in pregnancy

Because TSH is normally the most sensitive measure of thyroid function, initial biochemical diagnosing of hyperthyroidism often consists of measuring TSH, and if this is below the reference interval, then total T_4 /free T_4 and total T_3 /free T_3 (21). Such type of biochemical diagnosing of thyroid dysfunction depends on the normal function of the thyroid pituitary feedback system, and the fact that small changes in T_4 and T_3 leads to relatively larger changes in serum TSH (22).

However, early pregnancy creates fundamental changes in thyroid physiology that may hamper the use of thyroid function test for exact diagnosing. In particular, the newly formed utero-placenta unit interferes strongly with normal pituitary-thyroid function and the results of thyroid function testing. Three main mechanisms are in action as depicted in Table 1.

One mechanism is a high activity of the T_4 and T_3 inactivating deiodinase type 3 (DIO3) in the developing placenta and in the entire uterine wall shortly after blastocyte implantation that takes place in gestational week 4 (23, 24). The high DIO3 activity leads to a high concentration of the inactive T_4 metabolite reverse T_3 in maternal blood from very early pregnancy (25, 26). As judged from experiments performed in perfused human placenta lobes, DIO3 activity is the cause for the rather low transfer of maternal T_4 and T_3 across the placenta. In such perfusion studies, blocking of DIO3 by iopanoic acid increases placental transfer of T_4 from the maternal to the foetal side of the placenta nearly 3000-fold (27).

Excessive thyroid hormone deiodination by DIO3 may lead to hypothyroidism as observed in patients with DIO3

Table 1 Three main mechanisms leading to changes in early pregnancy thyroid function test results and the overall effects observed in women with and without an intact thyroid.

	TSH	Total T_4 and T_3	Free T_4 and T_3
Utero-placental DIO3 activation	↑↑	↓	↓
hCG secretion	↓↓↓	↑	↑
Oestrogen-induced TBG increase	↑	↑↑	↓
Overall effect ^a	↓↓	↑↑	↑
Intact thyroid			
Overall effect ^b	↑↑	↑	↓
No thyroid gland + replacement			

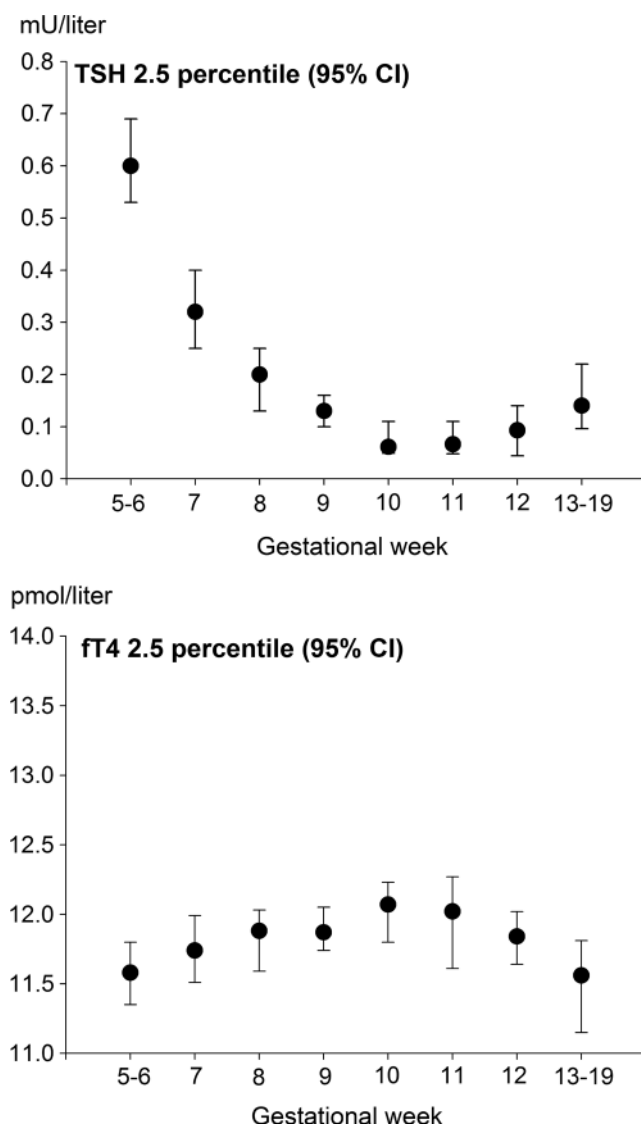
Arrows indicate direction and strength of variation, but are not precise indicators of magnitude.

^aEarly pregnancy variation in test result in a woman with a normal hypothalamic-pituitary-thyroid gland function; ^bEarly pregnancy variation in test result in a woman who has no functional thyroid gland, but who was euthyroid on levothyroxine replacement therapy before becoming pregnant.

expressing tumours (28). To keep the pregnant woman euthyroid despite the aggressive inactivation of thyroid hormone taking place in the utero-placenta, maternal thyroid hormone production has to increase. The simple clinical model to observe this early pregnancy need of an increase in thyroid hormone production is women with no thyroid gland, who are on stable thyroid hormone replacement therapy before becoming pregnant. To avoid an increase in serum TSH in early pregnancy, such women should increase their levothyroxine replacement dose from early pregnancy. The pregnancy associated increase in levothyroxine dose is in the order of 50% (29).

Another placenta product that affects thyroid function from early pregnancy is human chorionic gonadotropin (hCG). hCG has structural similarities to TSH (identical alpha-subunit) and it is a weak TSH-receptor agonist (30). hCG serum concentration increases dramatically in early pregnancy, and the high level stimulates the thyroid gland. Thus, opposite to the TSH variation seen in athyreotic women, women who have an intact thyroid tend to have a decrease in TSH in early pregnancy (31) despite their increase in need of thyroid hormone production discussed above.

In normal pregnant women, the high hCG effect clearly outweighs the high DIO3 effect from week 7 of pregnancy (Fig. 2 and Table 1), and both median TSH and upper and lower reference limits start decreasing (32, 33, 34, 35, 36). To emphasize that thyroid function test reference values are variable in pregnancy, but still keep evaluation somewhat simple, much focus has been

**Figure 2**

Gestational week-specific lower reference limit (2.5 percentile) for serum TSH and free T_4 in 6671 healthy Danish pregnant. Vertical lines are 95% confidence intervals for reference limit values. Reproduced with permission from Laurberg P *et al.* (36).

on defining 'trimester-specific reference limits' (6, 7). However, in the first trimester of pregnancy, the lower reference limit for TSH used to diagnose hyperthyroidism may vary from week to week of gestation (36), as illustrated in Fig. 2. Until and including gestational week 6, the non-pregnancy laboratory reference range for TSH can be used; in week 9–12, the lower reference limit of TSH is around 0.1 mU/L (or even below 0.1 mU/L in week 10–11); and between these time periods, the limit changes from week to week. In the second and third trimester of pregnancy,

the non-pregnancy lower reference limit for TSH can be used (37).

Free T_4 reference limits may be slightly higher (~5%) than non-pregnancy reference limits in pregnancy weeks 9–12 (Fig. 2). In the second and especially in the third trimester of pregnancy, the concentrations of free thyroid hormones become lower than non-pregnancy values (25). Correct free T_4 (and free T_3) analytical results are obtained with methods that include an initial isolation of the free hormone by ultrafiltration or dialysis followed by direct measurement of hormone in filtrate/dialysate by mass spectrometry (or sensitive radioimmunoassay). Methods are relatively complex and performance may not be perfect. The automated free T_4 and free T_3 assays used by routine laboratories do not separate the free fraction before analyses, and the estimates they give are prone to deviation from 'true free hormones' in many situations (38). One problem with these assays, when used in pregnancy, is the great variability in results obtained with assays from different manufacturers (39), which has led some experts to recommend not using these assays to diagnose and control thyroid disease in pregnancy (40).

An alternative is to use assays measuring total T_4 and total T_3 . In pregnancy, results of these assays change because of the third mechanism affecting thyroid function testing in early pregnancy, the oestrogen-induced increase in the serum concentration of thyroxine-binding globulin (TBG) (Table 1). TBG is the major thyroid hormone binding protein, and in a closed system, an increase in hormone binding will be associated with a decrease in free hormone concentration (Table 1). A gradual doubling in TBG concentration in serum takes place over pregnancy weeks 7–16 (41, 42), and this leads to a 50% increase in the concentrations of total T_4 and T_3 , with a corresponding increase in upper and lower reference ranges for these hormones (25). Thus, as a practical guide, reference limits for total T_4 and total T_3 increase with 50% of non-pregnancy values per week during the 10 pregnancy weeks 7–16, and remain 50% above non-pregnancy values during the remaining pregnancy.

To compensate the increase in bound T_4 (and T_3) during the week 7–16 period, a small increase has to take place in the thyroid hormone production. If it, in a simplified model, is assumed that the non-pregnancy serum pool of T_4 is 0.25 mg, then a 5% expansion per week corresponds to 12.5 μ g extra T_4 per week or 1.5–2 μ g per day. If it is assumed, in a less likely model, that not only the serum pool but the entire body pool of T_4 (1 mg) is expanded with 50%, this corresponds to 7 μ g per day. Thus, the TBG increase contributes moderately to the

increase in need of L-T₄ replacement dose in athyreotic pregnant patients (Table 1) (29).

Diagnosing Graves' disease in pregnancy

In principle, the biochemical diagnosing of hyperthyroidism is straightforward. A serum TSH below the reference range with serum T₄ and/or T₃ values above the laboratory reference range characterizes overt hyperthyroidism, whereas subclinical hyperthyroidism shows low TSH, but T₄ and T₃ values within the reference range (21). As discussed above, interpretation may be challenged in pregnancy by dynamic changes in assay reference limits, and often precise reference limit values for the specific assays used are not available. If there is doubt about the biochemical diagnosis of hyperthyroidism in early pregnancy, watchful observation with repeated testing is preferred to drug therapy, as discussed later in this review. In a US study of 25 765 women screened for thyroid dysfunction in early pregnancy, there was no association between biochemical subclinical hyperthyroidism and adverse pregnancy outcomes (43).

In the pregnant woman with biochemical and clinical symptoms and signs of hyperthyroidism, it is very important to consider the cause of the disease. In GD, there may be other disease manifestations (eye changes that are seen in about 25%, and goitre that is present in about 50% of patients with newly diagnosed GD (44)), and TSH receptor antibodies (TRAb) will typically be measurable (negative in a few percent of patients, mostly with mild disease (45)).

A common differential diagnosis to early pregnancy GD is gestational transient thyrotoxicosis (GTT), caused by the high levels of hCG. This is especially observed in women with hyperemesis (30), and TSH suppression may be more pronounced when maternal hCG is high such as in twin pregnancy (32, 46). GD and GTT are the common causes of thyrotoxicosis in pregnancy, but occasionally other causes are detected (47, 48).

Therapy of Graves' disease and the risk of birth defects

For many years, the standard recommended therapy of hyperthyroidism from GD in pregnancy has been one of the thionamide anti-thyroid drugs (methimazole (MMI) or its pro-drug carbimazole (CMZ), or propylthiouracil (PTU)). These drugs are effective in inhibiting the excessive thyroid hormone production of Graves' hyperthyroidism, both in pregnant and in non-pregnant patients.

One problem with the drugs is that severe side effects may occur, and the most common are agranulocytosis and liver failure. After it turned out that PTU was the third most common cause of drug-induced liver failure with a need of transplantation in the USA (49), guidance came out to use PTU for therapy of hyperthyroidism only in special circumstances. One of these special circumstances was early pregnancy, because rare cases of birth defects had been described after the use of MMI/CMZ, but not after the use of PTU (50).

The first report on birth defects after the use of thionamide anti-thyroid drugs in pregnancy was a brief letter in 1972 describing aplasia cutis in the offspring after maternal use of MMI (51). After this, various other types of birth defects were reported, including special facial features. This leads to the description of a MMI/CMZ embryopathy (52, 53), considered to be very rare (54).

In recent years, large studies from Japan (55, 56) and Denmark (57, 58) have shown that MMI/CMZ-associated birth defects are more common than anticipated, and may affect ~1/30 of children exposed to the drug in the weeks 6–10 of pregnancy. This is considerably below 10% of the effect of thalidomide, the prime drug example of teratogenicity (59), but still enough to raise serious concern. Figure 3 illustrates the risk of various types of defects observed after MMI/CMZ exposure. In this study, the highest relative risk was seen for various types of abdominal wall defects (Fig. 3), followed by skin defects (aplasia cutis), digestive (oesophageal and other atresias), eye, urinary tract, respiratory (choanal atresia), and circulatory (ventricular septum) defects (57, 58).

The Danish study (57) also observed an increase in risk after exposure to PTU (~1/40 of exposed) (Fig. 3). Overall, the defects were less severe than the MMI/CMZ-associated defects (60), and they consisted of face and neck malformations (preauricular sinus and cysts), and urinary tract malformations (confined to boys). Some uncertainty has existed in this area of research, because some investigators found no association between ATD use in pregnancy and birth defects (61, 62, 63, 64). As recently reviewed in detail (65), the cause for the negative findings likely resides with the methods used in the studies. For example, the PTU-associated defects are relatively mild, and they are often not diagnosed immediately after birth, but first later when they lead to complications such as infections. Thus, studies relying solely on birth defects detected in newborns will not find association with the use of PTU, and also many of the MMI-associated malformations will not be detected (65). The majority of the Danish cases of PTU-associated defects had been

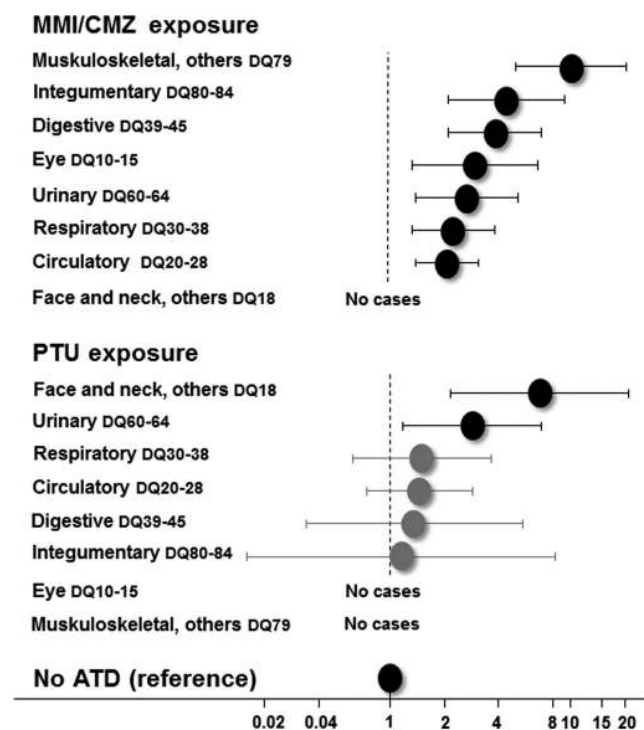


Figure 3

Adjusted odds ratio for developing various types of birth defects after early pregnancy exposure to methimazole or carbimazole (upper panel) or propylthiouracil (lower panel). Reference was children born to mothers who never received ATD therapy. In the PTU-exposed group, 'face and neck, others' were preauricular sinus and cysts. In the methimazole group, 'musculoskeletal, others' were various types of abdominal wall defects, 'integumentary' included aplasia cutis, 'digestive' included esophageal atresia, 'respiratory' included choanal atresia and 'circulatory' was ventricular septal defect. Reproduced with permission from Andersen SL *et al.* (57).

detected and registered when the children developed complications and received surgery for the defect later in childhood (60).

A review of cases where defects had been observed after start or stop of ATD therapy in pregnancy or after a shift of therapy from MMI to PTU revealed that the major period of exposure risk was gestational weeks 6–10, which is the period of organ formation, and the period of major risk from other teratogenic drugs (66).

Untreated overt hyperthyroidism may severely affect the health of a pregnant woman (67, 68) and it associates with foetal loss (4). Thus, overt hyperthyroidism in pregnancy has to be treated, and there should not be a universal ban on the use of ATDs in early pregnancy.

On the other hand, consideration on treatment strategy is appropriate. In general, around 6% of children have a birth defect diagnosed before 2 years of age (66). The 3–4% prevalence of birth defects associated with the use of PTU and MMI/CMZ in weeks 6–10 of pregnancy brings the prevalence to 9–10% in ATD-exposed children.

Pre-pregnancy counselling

A discussion on the possibility of a future pregnancy is obligatory when treating GD in women that may potentially become pregnant. The advantage of primary ablative therapy (radioiodine or surgical thyroidectomy) is that this will eliminate the risk of side effects from ATD. The drawbacks are the need for life-long thyroid hormone replacement (with the need of dose adjustment in pregnancy (29), which may be inadequate (69)), the risk of surgical side effects, and the tendency of radioiodine therapy to induce worsening of GD autoimmunity (70), with an increase in risk of Graves' orbitopathy (71). As discussed below, the TRAb increase after radioiodine may theoretically increase the risk of isolated foetal hyperthyroidism and neonatal transient hyperthyroidism from maternal TRAb.

Women who prefer ATD therapy to avoid the risk of side effects from surgery and radioiodine should be informed in detail on measures in relation to a possible future pregnancy (72). In our opinion, such women should be instructed to have at-home test kits to diagnose pregnancy from high urinary hCG. Such tests are positive early in the fifth week of pregnancy, which in women with a regular pattern of menstruation is the first week of a missing menstruation. If pregnancy is possible, the patient should perform a test, and if the test is positive, she should immediately contact the physician in charge of her thyroid therapy to make a plan.

If the physician considers the GD to be in remission based on (i) the results of recent thyroid function testing and TRAb measurement, (ii) the need of only a low dose of ATD, and (iii) the clinical condition, we suggest ATD withdrawal in gestational week 5. After stopping ATD, we suggest to arrange weekly thyroid function testing during the remaining first trimester. Notably, test results and clinical thyroid status should be evaluated in relation to gestational week as discussed in the first section of this review.

If ATD has to be started/restarted in early pregnancy to treat overt hyperthyroidism, the drug of choice is PTU, because the risk of severe birth defects is lower than with the use of MMI/CMZ (57, 60). An argument against the

use of PTU is the risk of liver failure (49, 50, 73). However, numerically the risk of ATD-associated liver failure or agranulocytosis in pregnancy is much lower than the risk of birth defects. Figure 4 illustrates the results of a Danish study that compared overall risk of agranulocytosis and liver failure with the overall risk of birth defects in the population (74). Risk of agranulocytosis and birth defects were quite similar, and considerably higher than the risk of liver failure. However, if focus was only on side effects from the use of ATD in pregnancy, the frequency of birth defects was around 75 times higher than the other types of severe side effects (Fig. 4).

In a subset of women becoming pregnant while treated with ATD for GD, the risk of hyperthyroidism relapse will be unacceptably high if ATD is withdrawn (75). This will be women who started ATD therapy recently (<6 months), who still have suppressed TSH, who have a relatively high serum T_3 (76), high levels of TRAb, large goitre, active orbitopathy, or other signs of active disease. In such women, MMI/CMZ should be replaced with PTU in early pregnancy (preferably in gestational week 5), using a dose ratio of 1:20 (77, 78, 79), e.g. 200 mg PTU per day replaces

10 mg MMI (or 15 mg CMZ). Because the half-life of PTU is considerably shorter, 10 mg MMI once daily corresponds to 100 mg PTU twice daily.

In women who actively plan pregnancy while being treated with an anti-thyroid drug, it may be appropriate to use PTU for therapy already before conception. This should be weighed against the higher (but low absolute) risk of severe liver failure during PTU therapy.

Alternative therapies for Graves' hyperthyroidism in early pregnancy

In pregnant women with mild hyperthyroidism in whom conventional ATD may not be necessary (and is not attractive) in early pregnancy, it may be speculated if other types of therapy could be used. In Japan, iodine therapy has been successfully used to treat hyperthyroidism in pregnancy (14, 56), with a significant reduction in birth defects compared with MMI therapy in a retrospective study (Fig. 5) (56). In this Japanese study, a sub-group of the women had worsening of hyperthyroidism after shift from MMI to iodine therapy, but despite this, there was no increase in pregnancy loss in the iodine-treated group (Fig. 5). Initial doses were 10–30 mg iodide per day given as potassium iodide (KI) tablets or solution and adjusted according to effect. Similar to extensive experiences from outside Japan at the time thionamide drugs became available, iodine therapy is clearly less effective than ATD in patients with severe GD (80). Iodine therapy may especially be useful during the major teratogenic period of ATDs (week 6–10), but more data on outcomes from controlled prospective studies are needed.

Another type of therapy that may be considered during early pregnancy in women with mild GD is cholestyramine (1–2 g 3–4 times per day). Cholestyramine has been used to treat intrahepatic cholestasis in pregnancy (81, 82). It is not absorbed from the gut, but it binds thyroid hormones during their enterohepatic circulation and thereby decreases circulating T_4 and T_3 in hyperthyroidism (83, 84, 85, 86, 87). Common side effects are nausea and other types of gastrointestinal discomfort, and there has been concern about binding of fat-soluble vitamins (especially vitamin K) during prolonged use. No experience with the use of cholestyramine to treat hyperthyroidism in early pregnancy has been published.

Perchlorate competitively inhibits the sodium-iodide-symporter (NIS), and it has been used to treat hyperthyroidism (88). Apparently, it has no teratogenic effects (89), but safety data from large studies using

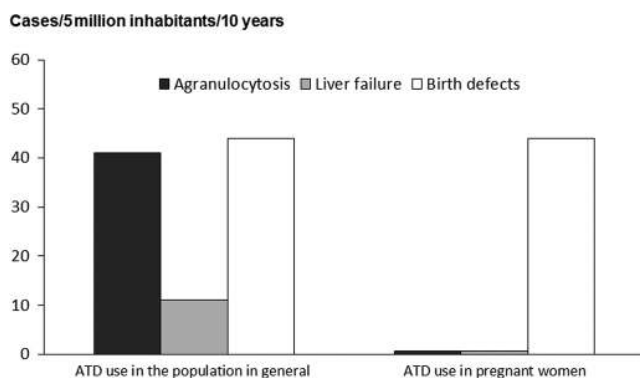
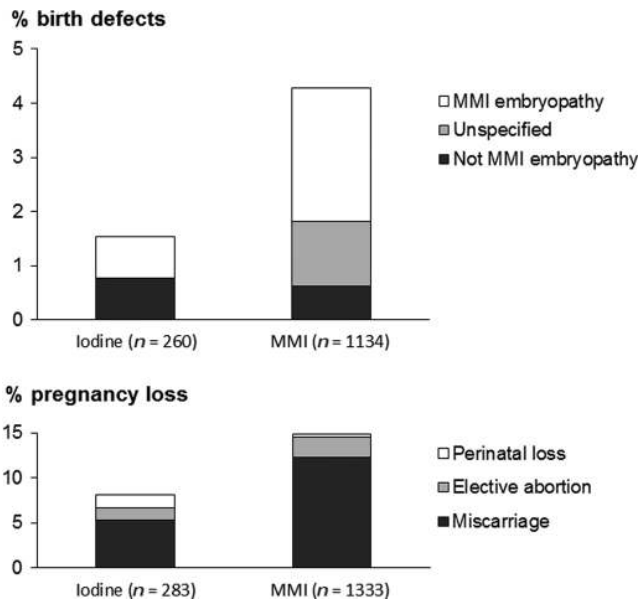


Figure 4

Cases of ATD-associated agranulocytosis, liver failure and birth defects in a Danish population-based study. Columns to the left illustrate number of ATD-associated cases identified among 50 million person-years in the general Danish population (including pregnant). Columns to the right illustrate ATD-associated cases when focusing only on the use of ATD therapy in pregnancy. Because birth defects are only observed after the use of ATD in pregnancy, the two white columns are identical. In the population, the occurrence of agranulocytosis and birth defects are about the same, and more common than liver failure. The dominating side effect after the use of ATD in pregnancy is birth defects. Data from Andersen SL *et al.* (74) used with permission.

**Figure 5**

Frequency of birth defects and of pregnancy loss in a retrospective Japanese study of pregnant with GD who were either treated with methimazole (MMI) or shifted from methimazole to iodine therapy in early pregnancy. Based on the data published (56), we stratified birth defects into those observed with a significant increase in frequency after methimazole exposure in the Danish study (Figure 3) (57) ('MMI embryopathy'), those not associated with methimazole exposure in the Danish study ('not MMI embryopathy'), and those where the description of cases in the Japanese study does not allow for such stratification ('unspecified'). Pregnancy loss was stratified according to the description of cases given in the Japanese study (56).

therapeutic doses are not available. There has been concern about teratogenicity of lithium (90) and it should not be used to treat hyperthyroidism in early pregnancy.

If alternative medical therapies are used off-label in early pregnancy, a shift to conventional ATD might be considered in mid-pregnancy, if therapy is still needed. At this time, many women with GD start entering remission and over treatment should be avoided, as discussed below. Surgery for GD is not recommended in pregnancy, but may occasionally be necessary. Optimally, it should be performed in late second trimester (6, 7).

Foetal hyper- and hypo-thyroidism

In pregnant women with GD, the condition of the foetus should be in focus (91). The foetal thyroid gland

starts to concentrate iodide in gestational week 10–12, but during the first half of pregnancy, the thyroid hormones involved in foetal development are nearly entirely of maternal origin. The TSH receptor stimulating antibodies that induce maternal hyperthyroidism will pass the placenta and may induce foetal hyperthyroidism from around week 20 (or even some weeks earlier in severe cases (92)). In principle: when the mother is suffering from Graves' hyperthyroidism, the foetus is also hyperthyroid. Fortunately, the ATDs used to treat maternal hyperthyroidism also pass the placenta, and when the hyperthyroidism of the mother is treated, the hyperthyroidism of the foetus is also treated. However, both MMI/CMZ and PTU (15) (and iodine (14)) tend to overtreat the foetus when the mother is made euthyroid. Thus, the dose of drug given to the mother should be as low as possible and maternal TSH should remain below the reference range. If the mother becomes TRAb negative, attempts should be made to withdraw ATD therapy.

The so-called block+replacement (ATD+levothyroxine) therapy should not be used in pregnancy, except in isolated foetal hyperthyroidism, discussed below. The principle of block+replacement is to overtreat the hyperthyroidism with ATD, and to keep the patient euthyroid by adding levothyroxine to therapy. If used to treat a pregnant woman with Graves' hyperthyroidism, the high dose of ATD will overtreat the foetal hyperthyroidism from mid-pregnancy, and the levothyroxine given to the mother will have only minimal effect in the foetus. The induced foetal hypothyroidism may be severe (91).

A special case is the isolated foetal hyperthyroidism that may develop in women who previously received ablative therapy for GD, but still produce high levels of TRAb. Foetal loss in such patients has been repeatedly reported. To detect such a risk, women who previously received ablative therapy for Graves' disease should have TRAb measured in early pregnancy. If TRAb is elevated, a program of biochemical and clinical follow-up has to be planned. These are the only women who should potentially receive block+replacement therapy in pregnancy (93). ATD to treat the isolated foetal hyperthyroidism via transplacental ATD transfer from the mother, and levothyroxine to keep the previously thyroid-ablated mother euthyroid.

There are other details to consider in a pregnant woman with GD. One is the risk of delayed neonatal hyperthyroidism if the mother has active and ATD-treated GD until delivery (94). Such risk is detected by measuring TRAb in the mother in late pregnancy (TRAb > three times above upper reference indicates risk

(95, 96)). Another consideration is the risk of GD relapse post-partum in women who experienced remission of GD in late pregnancy, and women who were in remission already before the pregnancy after previous ATD therapy. Post-partum relapse of GD has to be distinguished from thyrotoxicosis caused by post-partum thyroiditis (97). Severe thyrotoxicosis from post-partum thyroiditis tends to develop within the first 3 months post-partum (97), and the thyrotoxic condition tends to be soon replaced by hypothyroidism. GD most often develops more than 3 months after giving birth (Fig. 1), and patients may have eye signs. Moreover, TRAb is normally positive in GD and serum T_3 more elevated than serum T_4 (98). Measurement of thyroid blood flow by Doppler ultrasonography may assist to distinguish the two types of disease (97).

Conclusion

Adequate amounts of thyroid hormones are very important for successful pregnancy. Thus, any therapy of Graves' disease in a young woman should take the possibility of a future pregnancy into account. Women who are treated with ATD for Graves' disease should be prepared to diagnose pregnancy as early as possible, and to contact the physician responsible for their thyroid therapy immediately, if pregnancy is diagnosed. A plan for continuing/discontinuing ATD in pregnancy should optimally be made and executed already in week 5 of pregnancy. It is the responsibility of the treating physicians to educate patients accordingly, and health care providers should be prepared to act when contacted by a newly pregnant patient treated with ATD for GD.

Declaration of interest

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