THERAPY OF ENDOCRINE DISEASE

Antithyroid drug use in early pregnancy and birth defects: time windows of relative safety and high risk?

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Abstract

Background: Antithyroid drugs (ATDs) may have teratogenic effects when used in early pregnancy.

Objective: To review the association between the time period of ATD exposure in early pregnancy and the development of birth defects.

Methods: We identified publications on birth defects after early pregnancy exposure to the ATDs methimazole (MMI; and its prodrug carbimazole (CMZ)) and propylthiouracil (PTU). Cases of birth defects after ATD treatment had been initiated or terminated within the first 10 weeks of pregnancy were identified and studied in detail.

Results: A total of 92 publications were read in detail. Two recent large controlled studies showed ATD-associated birth defects in 2–3% of exposed children, and MMI/CMZ-associated defects were often severe. Out of the total number of publications, 17 included cases of birth defects with early pregnancy stop/start of ATD treatment, and these cases suggested that the high risk was confined to gestational weeks 6–10, which is the major period of organogenesis. Thus, the cases reported suggest that the risk of birth defects could be minimized if pregnant women terminate ATD intake before gestational week 6.

Conclusion: Both MMI and PTU use in early pregnancy may lead to birth defects in 2–3% of the exposed children. MMI-associated defects are often severe. Proposals are given on how to minimize the risk of birth defects in fertile women treated for hyperthyroidism with ATDs.

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Introduction

Hyperthyroidism in pregnancy may seriously hamper the health of the pregnant woman, interfere with the development of the fetus, and threaten fetal survival. Thus, planning and control of therapy for hyperthyroidism in a woman who is or in the future may become pregnant is a major concern (1, 2, 3, 4). The dominating cause of hyperthyroidism in women of fertile age is Graves' disease (5), and antithyroid drug (ATD) therapy is commonly used to achieve euthyroidism and a gradual remission of the autoimmune aberration of Graves'

disease (6). However, the ATD methimazole (MMI) and its prodrug carbimazole (CMZ) may have teratogenic effects (7, 8, 9, 10, 11), and recently it has been shown that children who have been exposed to propylthiouracil (PTU) during the period of organogenesis are also at an increased risk of having some specific birth defects (11). In general, major structural defects are observed in ~3% of neonates (12) and additional birth defects are detected later. Thus, the prevalence of identified birth defects approximates to 6% in 2-year-old children (12).

The first publication on a possible teratogenic effect of ATDs was a 13-line-long letter published in 1972 by Milham & Elledge (13) reporting that among 11 mothers giving birth to newborns with scalp defects, two mothers had been treated with MMI during the pregnancy for hyperthyroidism (one of the mothers delivered twins both of whom had scalp defects). More cases of aplasia cutis after MMI exposure were reported, and in 1994 Mandel *et al.* (14) concluded in a review that there was insufficient evidence either to establish or to eliminate a direct causal relationship. After this, more cases were published including, now also, more severe birth defects leading to the term methimazole/carbimazole embryopathy (7, 8), as described in several reviews (9, 15). Still, some studies have been negative (16, 17), and until recently, the additional risk of birth defects after early pregnancy use of MMI/CMZ was considered to be very low (2, 3). PTU was considered not to be teratogenic (2, 3), even if some non-human studies were positive (18, 19). However, two recent large controlled studies have shown that the risk is not negligible (10, 11).

Two new large studies substantiate birth defects after use of ATDs

A Japanese hospital record study published in 2012 (10) and a Danish National Registry study published in 2013 (11) both looked for birth defects in children born to mothers treated with MMI/CMZ in early pregnancy (Japan, $n=1426$ and Denmark, $n=1097$) compared with children born to mothers who had been treated for hyperthyroidism, but not in early pregnancy (Japan, $n=2065$), or children born to mothers who had never been treated for thyroid dysfunction (Denmark, $n=811\ 730$). Some other important methodological differences between studies are to be noticed.

The Japanese mothers were included if they had attended a specific hospital in Tokyo for Graves' disease. Depending on local referral patterns, this may to some extent have selected patients with more severe Graves' disease (20). The Danish study included all live-born Danish children over a period of time. In the Japanese study, mothers had been interviewed about the presence of birth defects at the first consultation after delivery. The Danish study included all types of birth defects that had been registered in Danish hospitals at in- and outpatient visits before the child was 2 years old. Thus, the Danish study also included minor birth defects and birth defects that were not detected immediately at birth. A major strength of the Japanese study was knowledge of the dose

of the ATD given in early pregnancy, and information on the thyroid function of the mother during the period. Notably, neither abnormal maternal thyroid function nor the dose of the ATD taken by the mother in early pregnancy influenced the risk of birth defects in multivariate analyses.

The results of the two studies were quite similar regarding the risk of birth defects after MMI exposure. In Japan, an additional 2.0% of children (controls, 2.1% and MMI-exposed, 4.1%) had defects, and in Denmark this was 3.4% (controls, 5.7% and MMI/CMZ-exposed, 9.1%) ($P<0.001$ in both studies). Owing to the different methods used to record birth defects, the frequency of birth defects was in general higher in the Danish study. In both studies, about half of the excess cases were caused by the types of birth defects described previously under the term 'methimazole/carbimazole embryopathy' (7, 8). They were especially aplasia cutis, omphalocele, omphalomesenteric duct anomaly, choanal atresia, and esophageal atresia. As the Danish study included the large control group, this study had more statistical power to detect subgroups of birth defects and defects with a low prevalence, and the study also found a significantly higher risk of circulatory (primarily confined to heart septal defects), eye, and urinary birth defects after MMI/CMZ exposure in early pregnancy.

A major difference in study results was the association between PTU exposure in early pregnancy and birth defects. In the Japanese study, no such association was observed, whereas the Danish study found an overall increase in risk with an additional 2.3% of exposed children having birth defects. The PTU-associated birth defects appeared to be milder and were restricted to pre-auricular sinus/cyst and fistula and urinary system defects. Urinary system defects may coexist with pre-auricular malformations (21). The difference in findings between the two studies is likely to be caused by the difference in the recording of birth defects: early *post partum* maternal interview in Japan vs the recording of all diagnoses up to 2 years of age in Denmark. Moreover, the findings in relation to PTU in Denmark would not have been statistically significant, if the study had not included the large control group of more than 800 000 children born to mothers who were never treated for thyroid dysfunction.

Time windows of relative safety and high risk

The vast majority of reported cases of birth defects after pregnancy exposure to ATDs have occurred after ATD therapy in the first trimester of pregnancy (9, 15), which is the period of organogenesis as illustrated in Fig. 1 (12).

Figure 1

Schematic illustration showing the time period in gestational weeks of maximal sensitivity to abnormal development in humans. Note that no embryo is present during the 1st and 2nd gestational weeks, because the average time span from 1st day of last menstrual period to conception is 2 weeks. Thus, gestational weeks 6–10 correspond to embryological weeks 4–8. The figure is adapted from Moore *et al.* (12) with permission. Full colour version of this figure available via <http://dx.doi.org/10.1530/EJE-14-0135>

As MMI/CMZ, but not PTU, had previously been associated with a higher frequency of birth defects, it has been recommended to use PTU and not MMI/CMZ during the first trimester of pregnancy, and to shift from MMI/CMZ to PTU therapy in early pregnancy if the woman received MMI/CMZ before the pregnancy (2, 3). MMI/CMZ is the recommended therapy in non-pregnant patients, because it has a better pharmacodynamic profile and less severe side effects than PTU (22).

We have evaluated this recommendation with a special focus on the association between the time of ATD exposure in early fetal life and the risk of birth defects. Two sets of data will be presented and used for discussion, one set was retrieved from a systematic literature search and the other was derived from our Danish register study (11).

Shift between therapies in early pregnancy

We identified published cases of birth defects after ATD use in early pregnancy by a PubMed search using combinations of the drugs (antithyroid drugs/methimazole/carbimazole/propylthiouracil) AND birth

defects (birth defects/malformations/congenital malformations), followed by screening of abstracts, reading of articles, and inclusion of additional publications mentioned in the retrieved articles.

In addition to our Danish Registry study (11) to be discussed below, a total of 91 reports were read in detail, and 24 cases with ATD-associated birth defects where shifts in ATD therapy (start/stop of therapy or shifts between MMI/CMZ and PTU) had occurred during gestational weeks 1–10 were identified in 16 of the 91 publications (7, 8, 10, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35). Published gestational week (calculated from the 1st day of the last menstrual period) when start or stop of ATD treatment had occurred was retrieved from these publications.

Figure 2 shows the time of pregnancy (gestational week) when therapy with MMI/CMZ had been stopped or initiated in the 24 cases from the literature of children diagnosed with birth defects after having been exposed to MMI/CMZ during a period of the first 10 gestational weeks. All the types of defects included in this analysis have been found associated with MMI/CMZ exposure in several studies including dysmorphism with a characteristic facial appearance (7, 8) and urinary system defects (11).

As illustrated in Fig. 2, two cases of aplasia cutis have been reported after exposure that took place during, but not after, the first 4 weeks of pregnancy (10, 29). One of the cases had first been evaluated for publication a long time after exposure, at the age of 5 years (29). Apart from these two cases, all reports included exposure during gestational weeks 6–10. Notably, gestational weeks 6–10 estimated from the 1st day of last normal menstruation correspond to embryological weeks 4–8 because conception takes place ~2 weeks after the 1st day of the last menstrual period. Gestational weeks 6–10 are the period of major organogenesis (Fig. 1).

Therapy shifts in the Danish Registry study

In addition to the literature search, we investigated in detail the time of exposure and the type of birth defects in the 149 pregnant women in our previous Danish Registry study who had shifted from MMI/CMZ to PTU in early pregnancy (11). Our previous study had illustrated that a routine shift from MMI/CMZ to PTU may give little protection against birth defects, because 13 of the 149 children (8.7%) had birth defects (11).

Figure 3 illustrates the time of gestation at which the mothers of the 13 Danish children with defects had shifted from MMI to PTU. Cases with birth defects were stratified according to the type of birth defect. The upper

Figure 2

Data from a literature search. Symbols indicate the gestational week when start or stop of MMI/CMZ therapy was reported in 24 cases of MMI/CMZ-associated birth defects where change of medication had occurred in early pregnancy (7, 8, 10, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35). Symbols above the line indicate that MMI/CMZ exposure took place until the symbol.

row of the figure shows the time of shifting for the individual cases in which the birth defect belonged to a type associated with MMI/CMZ exposure in the study (11), and the second row with PTU exposure. Urinary defect (third row) was associated with both MMI and PTU exposure, whereas the types of birth defects depicted in the lower row were not significantly associated with either MMI or PTU in the Danish Registry study (11).

As depicted in Fig. 3, MMI-associated defects were only observed when a shift had been performed at or after 7 weeks of pregnancy, whereas the two PTU-related defects occurred when PTU had been started at 6 weeks of pregnancy. On the other hand, when defects were not related to MMI or PTU, shifts were more evenly distributed over time.

Table 1 shows the time of shift in various groups in the study (11). Compared with the group of children without birth defects, shifts had been performed 20 days later in the group with MMI-associated birth defects ($P=0.016$). On the other hand, the time of shift in relation to gestation was similar in the group without birth defects and the group with birth defects not related to MMI or PTU ($P=0.83$). Direct comparison of the time of shift in the group with MMI-type defects and the group with non-specific birth defects had low power because both groups included only five mothers, and the difference was not statistically significant in a two-sided test ($P=0.075$).

Even if the number of cases is limited, Fig. 3 suggests that PTU-associated defects might occur if PTU is given later than

Symbols below the line indicate that MMI/CMZ exposure took place after the symbol. Additional birth defects were recorded in some of the cases. A case of choanal atresia after stop of MMI at 7 weeks of pregnancy had started ATDs at 4 weeks of pregnancy (25), and a case of facial dysmorphism after stop of MMI at 5½ weeks of pregnancy had restarted MMI at 9 weeks of pregnancy (28).

gestational week 5, which is compatible with the main type of PTU-associated malformation taking place during gestational week 6 (36). In our previous study (11), three children had birth defects after early (gestational weeks 4 and 5) pregnancy shifts from PTU to MMI/CMZ. One child had a typical MMI/CMZ-associated defect (esophageal atresia, shift week 4), whereas the two other children had defects that were not associated with ATDs in the main study.

Taken together, Fig. 3 and Table 1 suggest a crucial importance of even a few weeks' delay in termination of MMI therapy. Moreover, based on the various findings in mothers who changed therapy in early pregnancy, it may be anticipated that termination of ATD therapy before the end of gestational week 5 will nearly eliminate the risk of both MMI- and PTU-associated birth defects.

Few cases have been reported that do not fit into the general pattern of the time of exposure. As already discussed (Fig. 2), two cases of aplasia cutis were reported after MMI treatment had been given during the first 4 weeks of gestation only (10, 29). Furthermore, a neonate was reported to suffer from choanal atresia after exposure to MMI during gestational weeks 28–37 (31), and another neonate to have esophageal atresia with fistula to the trachea after maternal intake of MMI had been initiated at 14 weeks of gestation (37). All the types of birth defects seen after ATD use may also occur without ATD use. Thus, it is to be expected that some cases would not 'fit into the pattern'. Still, from the cases included in the present

Figure 3

Data from the Danish National Registry study on birth defects after early pregnancy use of ATDs (11). Arrows indicate the week of gestation when shift from MMI/CMZ to PTU had been performed in 13 children with birth defects. Patients were stratified according to the type of birth defect in the registry study (11): associated with early pregnancy MMI/CMZ therapy, with PTU therapy, with PTU or MMI/CMZ therapy, and not associated with ATD therapy. Time of shift and the type of birth defect in individual children is indicated by arrows. Data adapted from Andersen *et al.* (11).

review, it cannot be excluded that there is some risk of aplasia cutis even after exposure to MMI/CMZ before week 5 and also after week 10.

Apparently, there is little or no association between the dose, within the dose range used for therapy, of ATDs used and the risk of birth defects (10, 31, 32). One Japanese study published in 1984 found that only two out of six hyperthyroid mothers giving birth to children with defects had received MMI in early pregnancy, and it was proposed that hyperthyroidism and not the drug was the main cause for the increase in risk of birth defects (38). However, this conclusion is not supported by the more recent and much larger Japanese study (10). Furthermore, the very different patterns of birth defects in patients treated with MMI/CMZ and PTU (11) are a strong argument against maternal hyperthyroidism being the main cause for the defects observed, and in a large part of the cases reported after the use of MMI/CMZ the mother was euthyroid in pregnancy.

Withdrawal of ATD therapy in early pregnancy

The autoimmune abnormality leading to hyperthyroidism in Graves' disease tends to gradually enter remission during ATD therapy, as discussed previously (39), with the disappearance of TSH receptor auto-antibodies from serum (6). If ATD therapy is withdrawn after 12–18 months of therapy, around half of patients will experience a relapse of hyperthyroidism, but normally relapses will not develop immediately. In a prospective study performed in Sweden, only two out of 16 (non-pregnant) patients who had a relapse of hyperthyroidism during 3.5 years of follow-up after termination of 18 months of ATD therapy became hyperthyroid within 2 months after drug withdrawal (6).

Figure 4 illustrates a case of severe birth defects of the 'methimazole/carbimazole embryopathy' type from the Danish study (11). The woman had first received block+replacement therapy for hyperthyroidism for 2 years. This is a common type of therapy for Graves' hyperthyroidism in Denmark (40). After withdrawal of medication, she received no medication for another 2 years before again starting treatment with MMI+levothyroxine (L-T₄), which was given for another 2-year period. Before the withdrawal of ATD treatment, the patient became pregnant, and the last MMI prescription was redeemed in gestational week 8. During the second and third trimesters of pregnancy, no thyroid medication was prescribed. Delivery was at week 35. Apparently, hyperthyroidism relapsed *post partum*, and the patient was again treated with block+replacement. Finally, surgical thyroidectomy was performed (as shown in Fig. 4).

At birth, the neonate had severe MMI embryopathy and was diagnosed with choanal atresia, esophageal atresia

Table 1 Days of gestation when shift from MMI to PTU had been performed in 149 mothers in a Danish Registry study on ATD use and birth defects. Data adapted from Andersen *et al.* (11).

	n	Days of gestation		
		Median	95% CI range ^a	P*
All children	149 ^b	44	41–47	–
No birth defects	136	43	40–46	–
MMI-type birth defects ^c	5	63	50–69 ^d	0.016
Non-specific birth defects	5	40	24–58 ^d	0.83

*P value for the comparison with the group without birth defects (Mann–Whitney U test).

^a95% CI of median.

^bIncludes two cases with PTU-type birth defects and one case with hydronephrosis (both MMI- and PTU-associated).

^cMMI-type vs non-specific birth defects; P=0.075.

^dUpper limit held at maximum.

Figure 4

Case of 'methimazole/carbimazole embryopathy' from the Danish study on birth defects (11). Intervals on the horizontal line are years. Arrows indicate redeemed prescriptions of methimazole (MMI) and levothyroxine (L-T₄), start of pregnancy (pregnant), birth of child at gestational week 35 (birth, week 35), and the time of surgical thyroidectomy of the mother (Tx). Week 8 indicates that the last MMI prescription in pregnancy was redeemed at

with tracheal fistula, jejunal atresia/stenosis, kidney cysts, omphalocele, and cardiac defects (ventricular and atrial septal defects). Subsequently, inpatient hospital contact with these diagnoses was nearly continuously registered for more than 1 year, and >20 surgical procedures had been registered before the child died. Based on the data reviewed above, it may be speculated that these severe malformations might not have occurred if the MMI therapy had been terminated already in gestational week 5.

The mother presented in Fig. 4 was treated using a combination of MMI and L-T₄ (block+replacement therapy), which should in general not be used in pregnancy, as it may lead to fetal hypothyroidism (1). Moreover, the dose of ATDs used in combination would tend to be higher than the dose of ATDs given as monotherapy. Even if there is no indication of an ATD dose effect on the risk of birth defects at present, as discussed above, clear dose effects have been observed after the use of other types of teratogenic drugs (12).

In a case like this, the mother would probably have remained euthyroid for the remaining pregnancy after ATD withdrawal in gestational week 5, and at least she would have had a high probability of staying euthyroid without ATD treatment for the following 6 weeks when fetal organogenesis took place (Fig. 1). If biochemical signs of overt hyperthyroidism had developed, therapy could have been given with PTU, which appears to be associated with less severe birth defects (11), or if in Japan with pharmacological doses of iodine (41). Unfortunately, there

is little recent experience with prolonged iodine therapy for hyperthyroidism in pregnancy outside of Japan.

gestational week 8. The two boxes indicate our interpretation of a planned 2-year block + replacement therapy, which is a common type of therapy for Graves' hyperthyroidism in Denmark (40). The neonate was diagnosed with choanal atresia, esophageal atresia with tracheal fistula, jejunal atresia/stenosis, kidney cysts, omphalocele, and cardiac defects (ventricular and atrial septal defects). Data adapted from Andersen *et al.* (11).

Therapy for hyperthyroidism in fertile women

It is beyond the scope of the present review to discuss all aspects of therapy for Graves' hyperthyroidism in fertile and pregnant women (1, 2, 3, 4). The risk of birth defects after use of ATDs in early pregnancy may support the use of other types of therapy in some patients. Radioiodine is not to be used during or immediately before pregnancy,

Table 2 Proposed measures to reduce the number and severity of antithyroid drug (ATD)-associated birth defects.

1. Restrict the use of ATDs in first trimester (weeks 6–10) of pregnancy
2. Give written instruction to fertile women treated with ATDs to:
 - i) Perform a pregnancy test within a few days after the 1st day of a missed (or atypical week) menstrual period, if pregnancy is a possibility
 - ii) If the pregnancy test is positive, contact physician the same day, and take no more ATDs before such contact
3. If the pregnant woman is considered in remission of Graves' disease, observe without ATDs along with weekly thyroid function testing until second trimester
4. If an ATD is necessary in early pregnancy: use PTU
5. If future pregnancy is planned: consider shift from MMI/CMZ to PTU before pregnancy
6. Consider surgical therapy in young women with severe Graves' disease

and the tendency of radioiodine therapy to be followed by a long-lasting increase in serum concentrations of thyroid-stimulating antibodies may increase the risk of fetal and neonatal hyperthyroidism during a subsequent pregnancy (6). Thus, we would consider surgical thyroidectomy a better solution in young women with severe Graves' hyperthyroidism that shows little tendency to remission during ATD therapy. In retrospect, surgical thyroidectomy might have been an optimal therapy at first relapse of hyperthyroidism in the patient illustrated in Fig. 4.

The use of ATDs during gestational weeks 6–10 should be restricted as much as possible, as outlined in Table 2. In a large study (42), low serum TSH in early pregnancy corresponding to subclinical hyperthyroidism in a non-pregnant patient was not associated with adverse pregnancy outcomes, and such patients should not be treated with ATDs.

When ATD therapy is given to fertile women, we propose that a written instruction is given to the patients (Table 2). In our opinion, patients should be instructed to perform a pregnancy test within a few days (maximum 1 week) after the 1st day of a missed menstrual period, if pregnancy is a possibility. According to specifications from Danish pharmacies (www.apoteket.dk), self-administered pregnancy tests have turned positive in 99.9% of pregnancies already at the 2nd day of a missing menstrual period caused by pregnancy.

If the pregnancy test is positive, patients should immediately contact their physician and take no more ATDs before such contact. The physician contacted should evaluate, if it is feasible to observe without therapy, but with weekly thyroid function testing for the remaining part of the first trimester of pregnancy. If ATD therapy has already been given for more than 6–12 months and recent thyroid function tests have been normal, close observation without ATD therapy will probably often be sufficient during the critical period of organogenesis. If ATD therapy is necessary, PTU should be used, because birth defects after PTU therapy seem to be less severe.

It is important that women treated with an ATD know that untreated hyperthyroidism in pregnancy also involves a major risk of severe maternal and fetal complications and that close collaboration with the responsible physician is imperative.

We support the proposal that women who plan pregnancy are shifted from MMI to PTU already before the pregnancy (9), as previously recommended in Japan (43), even if concern has been raised on the risk of PTU-related MPO-ANCA-positive vasculitis in women who had previously received PTU (43). Moreover, the minimal risk of PTU-associated hepatic failure should be taken into account (44).

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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References

- Laurberg P, Bournaud C, Karmisholt J & Orgiazzi J. Management of Graves' hyperthyroidism in pregnancy: focus on both maternal and foetal thyroid function, and caution against surgical thyroidectomy in pregnancy. *European Journal of Endocrinology* 2009 **160** 1–8. (doi:10.1530/EJE-08-0663)
- Stagnaro-Green A, Abalovich M, Alexander E, Azizi F, Mestman J, Negro R, Nixon A, Pearce EN, Soldin OP, Sullivan S *et al.* Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and *postpartum*. *Thyroid* 2011 **21** 1081–1125. (doi:10.1089/thy.2011.0087)
- De Groot L, Abalovich M, Alexander EK, Amino N, Barbour L, Cobin RH, Eastman CJ, Lazarus JH, Luton D, Mandel SJ *et al.* Management of thyroid dysfunction during pregnancy and *postpartum*: an Endocrine Society clinical practice guideline. *Journal of Clinical Endocrinology and Metabolism* 2012 **97** 2543–2565. (doi:10.1210/jc.2011-2803)
- Cooper DS & Laurberg P. Hyperthyroidism in pregnancy. *Lancet. Diabetes & Endocrinology* 2013 **1** 238–249. (doi:10.1016/S2213-8587(13)70086-X)
- Carle A, Pedersen IB, Knudsen N, Perrild H, Ovesen L, Rasmussen LB & Laurberg P. Epidemiology of subtypes of hyperthyroidism in Denmark: a population-based study. *European Journal of Endocrinology* 2011 **164** 801–809. (doi:10.1530/EJE-10-1155)
- Laurberg P, Wallin G, Tallstedt L, Abraham-Nordling M, Lundell G & Torring O. TSH-receptor autoimmunity in Graves' disease after therapy with anti-thyroid drugs, surgery, or radioiodine: a 5-year prospective randomized study. *European Journal of Endocrinology* 2008 **158** 69–75. (doi:10.1530/EJE-07-0450)
- Clementi M, Di Gianantonio E, Pelo E, Mammi I, Basile RT & Tenconi R. Methimazole embryopathy: delineation of the phenotype. *American Journal of Medical Genetics* 1999 **83** 43–46. (doi:10.1002/(SICI)1096-8628(19990305)83:1<43::AID-AJMG8>3.0.CO;2-C)
- Foulds N, Walpole I, Elmslie F & Mansour S. Carbimazole embryopathy: an emerging phenotype. *American Journal of Medical Genetics. Part A* 2005 **132A** 130–135. (doi:10.1002/ajmg.a.30418)
- Taylor PN & Vaidya B. Side effects of anti-thyroid drugs and their impact on the choice of treatment for thyrotoxicosis in pregnancy. *European Thyroid Journal* 2012 **1** 176–185. (doi:10.1159/000342920)
- Yoshihara A, Noh J, Yamaguchi T, Ohye H, Sato S, Sekiya K, Kosuga Y, Suzuki M, Matsumoto M, Kunii Y *et al.* Treatment of Graves' disease with antithyroid drugs in the first trimester of pregnancy and the prevalence of congenital malformation. *Journal of Clinical Endocrinology and Metabolism* 2012 **97** 2396–2403. (doi:10.1210/jc.2011-2860)
- Andersen SL, Olsen J, Wu CS & Laurberg P. Birth defects after early pregnancy use of antithyroid drugs: a Danish Nationwide Study. *Journal of Clinical Endocrinology and Metabolism* 2013 **98** 4373–4381. (doi:10.1210/jc.2013-2831)
- Moore KL, Persaud TVN & Torchia MG. Human birth defects. In *The Developing Human: Clinically Oriented Embryology*, 9th edn, pp 471–501. Philadelphia, PA, USA: Saunders/Elsevier, 2013.

- 13 Milham SJ & Elledge W. Maternal methimazole and congenital defects in children. *Teratology* 1972 **5** 125–126. (doi:10.1002/tera.1420050117)
- 14 Mandel SJ, Brent GA & Larsen PR. Review of antithyroid drug use during pregnancy and report of a case of aplasia cutis. *Thyroid* 1994 **4** 129–133. (doi:10.1089/thy.1994.4.129)
- 15 Cassina M, Dona M, Di Gianantonio E & Clementi M. Pharmacologic treatment of hyperthyroidism during pregnancy. *Birth Defects Research. Part A, Clinical and Molecular Teratology* 2012 **94** 612–619. (doi:10.1002/bdra.23012)
- 16 Chen CH, Xirasagar S, Lin CC, Wang LH, Kou YR & Lin HC. Risk of adverse perinatal outcomes with antithyroid treatment during pregnancy: a nationwide population-based study. *BJOG: an International Journal of Obstetrics and Gynaecology* 2011 **118** 1365–1373. (doi:10.1111/j.1471-0528.2011.03019.x)
- 17 Korelitz JJ, McNally DL, Masters MN, Li SX, Xu Y & Rivkees SA. Prevalence of thyrotoxicosis, antithyroid medication use, and complications among pregnant women in the United States. *Thyroid* 2013 **23** 758–765. (doi:10.1089/thy.2012.0488)
- 18 Benavides VC, Mallela MK, Booth CJ, Wendler CC & Rivkees SA. Propylthiouracil is teratogenic in murine embryos. *PLoS ONE* 2012 **7** e35213. (doi:10.1371/journal.pone.0035213)
- 19 van Veenendaal NR, Ulmer B, Boskovski MT, Fang X, Khokha MK, Wendler CC, Blum M & Rivkees SA. Embryonic exposure to propylthiouracil disrupts left–right patterning in *Xenopus* embryos. *FASEB Journal* 2013 **27** 684–691. (doi:10.1096/fj.12-218073)
- 20 Carle A, Pedersen IB, Perrild H, Ovesen L, Jorgensen T & Laurberg P. High age predicts low referral of hyperthyroid patients to specialized hospital departments: evidence for referral bias. *Thyroid* 2013 **23** 1518–1524. (doi:10.1089/thy.2013.0074)
- 21 Leung AK & Robson WL. Association of preauricular sinuses and renal anomalies. *Urology* 1992 **40** 259–261. (doi:10.1016/0090-4295(92)90487-H)
- 22 Bahn Chair RS, Burch HB, Cooper DS, Garber JR, Greenlee MC, Klein I, Laurberg P, McDougall IR, Montori VM, Rivkees SA *et al.* Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. *Thyroid* 2011 **21** 593–646. (doi:10.1089/thy.2010.0417)
- 23 Díez-Delgado Rubio J, Belmonte Martín MJ, Calvo Bonachera MD & Lopez Candel E. Aplasia cutis as a teratogenic effect of methimazole. *Anales Españoles de Pediatría* 1999 **51** 290–292.
- 24 Rodríguez-García R. Bilateral renal agenesis (Potter's syndrome) in a girl born to a hyperthyroid mother who received methimazole in early pregnancy. *Ginecología y Obstetricia de México* 1999 **67** 587–589.
- 25 Di Gianantonio E, Schaefer C, Mastroiacovo PP, Cournot MP, Benedicenti F, Reuvers M, Occupati B, Robert E, Bellemin B, Addis A *et al.* Adverse effects of prenatal methimazole exposure. *Teratology* 2001 **64** 262–266. (doi:10.1002/tera.1072)
- 26 Ferraris S, Valenzise M, Lerone M, Divizia MT, Rosaia L, Blaid D, Nemelka O, Ferrero GB & Silengo M. Malformations following methimazole exposure *in utero*: an open issue. *Birth Defects Research. Part A, Clinical and Molecular Teratology* 2003 **67** 989–992. (doi:10.1002/bdra.10098)
- 27 Karg E, Bereg E, Gaspar L, Katona M & Turi S. Aplasia cutis congenita after methimazole exposure *in utero*. *Pediatric Dermatology* 2004 **21** 491–494. (doi:10.1111/j.0736-8046.2004.21417.x)
- 28 Valdez RM, Barbero PM, Liascovich RC, De Rosa LF, Aguirre MA & Alba LG. Methimazole embryopathy: a contribution to defining the phenotype. *Reproductive Toxicology* 2007 **23** 253–255. (doi:10.1016/j.reprotox.2006.11.007)
- 29 Baid SK & Merke DP. Aplasia cutis congenita following *in utero* methimazole exposure. *Journal of Pediatric Endocrinology & Metabolism* 2007 **20** 585–586. (doi:10.1515/JPEM.2007.20.5.585)
- 30 Iwayama H, Hosono H, Yamamoto H, Oshiro M & Ueda N. Aplasia cutis congenita with skull defect in a monozygotic twin after exposure to methimazole *in utero*. *Birth Defects Research. Part A, Clinical and Molecular Teratology* 2007 **79** 680–684. (doi:10.1002/bdra.20395)
- 31 Barbero P, Valdez R, Rodriguez H, Tiscornia C, Mansilla E, Allons A, Coll S & Liascovich R. Choanal atresia associated with maternal hyperthyroidism treated with methimazole: a case–control study. *American Journal of Medical Genetics. Part A* 2008 **146A** 2390–2395. (doi:10.1002/ajmg.a.32497)
- 32 Koenig D, Spreux A, Hieronimus S, Chichmanian RM, Bastiani F, Fenichel P & Brucker-Davis F. Birth defects observed with maternal carbimazole treatment: six cases reported to Nice's Pharmacovigilance Center. *Annales d'Endocrinologie* 2010 **71** 535–542. (doi:10.1016/j.ando.2010.07.001)
- 33 Douchement D, Rakza T, Holder M, Bonne NX & Fayoux P. Choanal atresia associated with tracheoesophageal fistula: the spectrum of carbimazole embryopathy. *Pediatrics* 2011 **128** e703–e706. (doi:10.1542/peds.2010-0945)
- 34 Gripp KW, Kuryan R, Schnur RE, Kothawala M, Davey LR, Antunes MJ, Reichard KW, Schneider A & Hall BD. Grade 1 microtia, wide anterior fontanel and novel type tracheo-esophageal fistula in methimazole embryopathy. *American Journal of Medical Genetics. Part A* 2011 **155A** 526–533. (doi:10.1002/ajmg.a.33705)
- 35 Ting YH, Zhou Y & Lao TT. Carbimazole embryopathy in a Chinese population: case series and literature review. *Birth Defects Research. Part A, Clinical and Molecular Teratology* 2013 **97** 225–229. (doi:10.1002/bdra.23117)
- 36 Tan T, Constantinides H & Mitchell TE. The preauricular sinus: a review of its aetiology, clinical presentation and management. *International Journal of Pediatric Otorhinolaryngology* 2005 **69** 1469–1474. (doi:10.1016/j.ijporl.2005.07.008)
- 37 Seoud M, Nassar A, Usta I, Mansour M, Salti I & Younes K. Gastrointestinal malformations in two infants born to women with hyperthyroidism untreated in the first trimester. *American Journal of Perinatology* 2003 **20** 59–62. (doi:10.1055/s-2003-38320)
- 38 Momotani N, Ito K, Hamada N, Ban Y, Nishikawa Y & Mimura T. Maternal hyperthyroidism and congenital malformation in the offspring. *Clinical Endocrinology* 1984 **20** 695–700. (doi:10.1111/j.1365-2265.1984.tb00119.x)
- 39 Laurberg P. Remission of Graves' disease during anti-thyroid drug therapy. Time to reconsider the mechanism? *European Journal of Endocrinology* 2006 **155** 783–786. (doi:10.1530/eje.1.02295)
- 40 Laurberg P, Buchholtz Hansen PE, Iversen E, Eskjaer Jensen S & Weeke J. Goitre size and outcome of medical treatment of Graves' disease. *Acta Endocrinologica* 1986 **111** 39–43. (doi:10.1530/acta.0.1110039)
- 41 Momotani N, Hisaoka T, Noh J, Ishikawa N & Ito K. Effects of iodine on thyroid status of fetus versus mother in treatment of Graves' disease complicated by pregnancy. *Journal of Clinical Endocrinology and Metabolism* 1992 **75** 738–744. (doi:10.1210/jcem.75.3.1517362)
- 42 Casey BM, Dashe JS, Wells CE, McIntire DD, Leveno KJ & Cunningham FG. Subclinical hyperthyroidism and pregnancy outcomes. *Obstetrics and Gynecology* 2006 **107** 337–341. (doi:10.1097/01.AOG.0000197991.64246.9a)
- 43 Kimura M, Seki T, Ozawa H, Ishihara T, Komatsu M, Tajiri S, Yanagi H, Nishina M, Noh JY, Fukagawa M *et al.* The onset of antineutrophil cytoplasmic antibody-associated vasculitis immediately after methimazole was switched to propylthiouracil in a woman with Graves' disease who wished to become pregnant. *Endocrine Journal* 2013 **60** 383–388. (doi:10.1507/endocrj.EJ12-0212)
- 44 Cooper DS & Rivkees SA. Putting propylthiouracil in perspective. *Journal of Clinical Endocrinology and Metabolism* 2009 **94** 1881–1882. (doi:10.1210/jc.2009-0850)

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