Antithyroid Drug Side Effects in the Population and in Pregnancy

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Objective: Methimazole (MMI) and propylthiouracil (PTU) are both associated with birth defects and may also rarely be associated with agranulocytosis and liver failure. The frequency of these side effects when antithyroid drugs (ATDs) are used in the population in general or in pregnancy remains to be elucidated.

Design: All individuals registered as the parent of a live-born child in Denmark, 1973–2008, were identified (n = 2 299 952) and studied from 1995 through 2010 for the use of ATDs. Outcomes were agranulocytosis, liver failure, and birth defects in their offspring. To evaluate the frequency of these side effects associated with the use of ATDs in pregnancy, all live-born pregnancies (n = 830 680), 1996–2008, were identified in a subanalysis.

Results: In the population studied, 28 998 individuals redeemed prescriptions of ATDs (exposure in 2115 pregnancies), which was associated with 45 cases of agranulocytosis (one in pregnancy) and 10 cases of liver failure (one in pregnancy). This corresponded to 41 and 11 cases of agranulocytosis and liver failure per 5 million inhabitants during a 10-year period (agranulocytosis: 0.16% of ATDs exposed [MMI: 0.11% vs PTU: 0.27%, $P = .02$]; liver failure: 0.03% of ATDs exposed [MMI: 0.03% vs PTU: 0.05%, $P = .4$]). The majority (83%) developed the side effect within 3 months of ATD treatment and 25% during hyperthyroidism relapse. The use of ATDs in pregnancy was associated with birth defects in 3.4% of exposed children (44 cases per 5 million inhabitants per 10 y), and the frequency of birth defects after ATD exposure was 75 times higher than both maternal agranulocytosis and liver failure in pregnancy.

Conclusions: In the Danish population in general, ATDs associated birth defects and agranulocytosis had similar frequencies and were more common than liver failure, whereas for the use of ATDs in pregnancy, birth defects were dominant. The burden of side effects to the use of ATDs can be reduced by restricting the use of ATDs in early pregnancy. (***J Clin Endocrinol Metab*** **101: 1606–1614, 2016)**

Untreated or inadequately treated hyperthyroidism in pregnancy may adversely impact the health of the pregnant woman and the development of the fetus (1). Thus, treatment of hyperthyroidism in pregnant women is imperative, but the use of antithyroid drugs (ATDs) in the teratogenic period of early pregnancy is associated with an increased prevalence of birth defects (2). Birth defects may be severe and may considerably influence the life of the child and the family. Consequently, the risk and type of birth defects associated with the use of methimazole (MMI)/carbimazole (CMZ) and propylthiouracil (PTU) are important to consider in clinical guidance on the management of maternal hyperthyroidism in pregnancy (3–5). The MMI/CMZ embryopathy including severe birth defects has been described for decades (6), whereas the finding that the use of PTU in early pregnancy also was asso-

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Abbreviations: ATD, antithyroid drug; CMZ, carbimazole; ICD, *International Classification of Disease*; MBR, Medical Birth Register; MMI, methimazole; PTU, propylthiouracil.

ciated with an increased prevalence of birth defects is brought forward in recent years (2). The types of birth defects associated with PTU appear to be less severe (2, 7). Thus, guidelines have recommended the use of PTU in the early pregnancy and that women treated with MMI/CMZ should be shifted to PTU at the first contact with their physician in pregnancy or even before pregnancy (3–5). ATD treatment may, however, also have other severe side effects of which the most frequent are agranulocytosis and liver failure (8). In the United States, several reports gave evidence on PTU associated severe liver failure, and this led to guidance to reduce the use of PTU with proposals to shift pregnant women from PTU to MMI/CMZ after the early pregnancy period (9, 10). The relative frequencies of these two types of severe side effects as opposed to the risk of birth defects associated with the use of ATD in pregnant women have, however, never been studied in the same population over the same period of time.

In a Danish nationwide cohort, we have examined the frequency of birth defects, agranulocytosis, and liver failure associated with the use of ATDs in the population in general and in pregnancy specifically. The aim of this evaluation was to assist guidance on the management of hyperthyroidism in general and particularly in pregnancy.

Materials and Methods

Study cohort

We used the Danish Medical Birth Register (MBR) (11) to identify all children born alive in Denmark from January 1, 1973, to December 31, 2008, and their parents (Figure 1). The MBR includes records on all births in Denmark including the personal identification number of the child and the parents (a 10 digit number assigned to all Danish residents and used in all the nationwide registers) (12). The study was approved by the Danish Data Protection Agency, and data were made available in Statistic Denmark in encrypted form so that no individuals could be identified. Approval by institutional review board and informed consent are not required for register-based studies in Denmark.

ATD exposure

Information on exposure to ATDs was evaluated from the registration of redeemed prescriptions of ATD in the Danish National Prescription Register (13). The Danish National Prescription Register contains individual information on all redeemed prescriptions (dispensed drugs) from Danish pharmacies since January 1, 1995. Each record includes the personal identification number, the date the prescription was redeemed, and the type of drug according to the Anatomical Therapeutic Chemical Classification System. The date the first prescription was redeemed was used to indicate the initial use of the drug. Only individuals who used ATDs before September 30, 2010, were considered ATD exposed (Figure 1). Relapse was defined by a period of more than 6 months between the successive redeemed prescriptions of ATDs. Information on radioiodine treatment was not available in the registers, but long-term L-T4 treatment and no registration of thyroid surgery after a diagnosis of ATD-associated agranulocytosis or liver failure was considered as a change in therapy to radioiodine.

Outcomes

Information on the outcomes under study was evaluated from the registration of hospital diagnoses in the Danish National Hospital Register (14). This register contains all diagnoses made and assigned in Danish hospitals (inpatients since 1977, in- and outpatients since 1995) using the *International Classification of Disease* (ICD) for coding (ICD, eighth revision, from 1977 through 1993, ICD, 10th revision, since 1994). We included all in- and outpatient visits from January 1, 1995, to December 31, 2010 (Figure 1). Agranulocytosis was defined by a diagnosis of agranulocytosis, aplastic anemia, or leucopenia excluding congenital or other specified types of disease (Figure 1). Liver failure was defined by a diagnosis of any noninfectious liver disease, and only toxic or acute liver failure was considered excluding alcoholic liver disease, chronic liver failure, or other specified type of liver disease (Figure 1). Birth defects were defined by a diagnosis of any birth defect (ICD, 10th revision: Q00-Q99.9) registered before the child was 2 years old.

Covariates

Information on covariates was obtained from the MBR and Statistic Denmark. The MBR contains information on gender and age of the parent at the time of a child's birth, and Statistic Denmark provided information on individual origin (born in Denmark/not born in Denmark). Information on the size, age, gender, and origin of the entire Danish population on January 1, 2003, was obtained from Statistic Denmark.

Statistical analyses

After linkage between exposure and outcome information, the following criteria were used to evaluate whether agranulocytosis and liver failure were associated with the use of ATDs: 1) the outcome was diagnosed after ATD treatment was initiated, 2) the outcome was diagnosed within 6 months after any redeemed prescription of ATDs, 3) the specific ATD was subsequently withdrawn, and 4) no other likely cause of the outcome appeared from an individual review of hospital diagnosis and redeemed prescriptions. The number of cases identified with ATD-associated agranulocytosis and liver failure in the study population (Figure 1) was standardized to the age distribution of the Danish population on January 1, 2003.

For the evaluation of agranulocytosis and liver failure associated with the use of ATDs in a pregnancy, the study population was restricted to women who gave birth to a live-born child in the years 1996–2008. ATD exposure in pregnancy was defined by redeemed prescription(s) of ATDs in the period ranging from 3 months before the estimated pregnancy start to the date the child was born. Because the study population included all live births in Denmark from 1996 through 2008, the number of cases identified with ATD-associated agranulocytosis or liver failure in pregnancy in the study population corresponded to the expected number of such cases in the Danish population and no standardization was performed. The frequency of side effects associated with the use of MMI/CMZ and PTU were compared using a χ^2 test or a Fisher's exact test as appropriate.

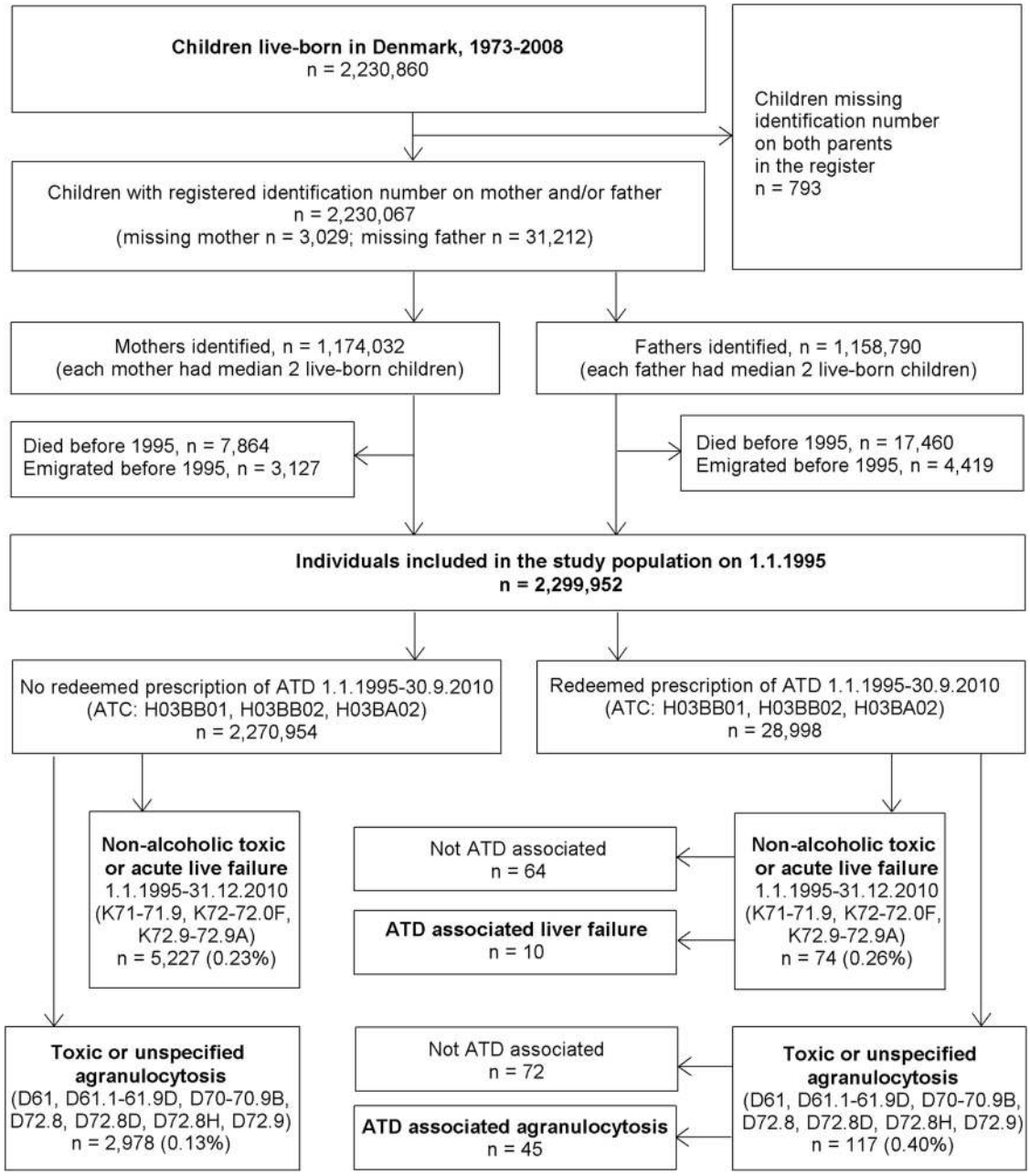

Figure 1. Flow chart illustrating the selection of the study population and the identification of cases of agranulocytosis and liver failure in the Danish nationwide registers associated with the use of ATD. ATC, Anatomical Therapeutic Chemical Classification System.

The method used to evaluate the frequency of ATD-associated birth defects has previously been described in detail (2). The present study included an almost identical study cohort, and details on the evaluation of ATD-associated birth defects in the present study are given in the Supplemental Materials and Methods.

Results

A total of 2 299 952 individuals were included in the study (Figure 1), representing nearly half of the entire Danish population on January 1, 2003 (Table 1). Gender distribution and the prevalence of individuals born outside Denmark were similar to the entire Danish population, but, as expected, the youngest and oldest age groups were underrepresented in the study population (Table 1).

In the population studied, 28 998 individuals redeemed prescription(s) of ATDs from 1995 through 2010 (Figure 1). The use of MMI/CMZ (n = 27 281) was more frequent than PTU (n = 5895) including a group of individuals who redeemed prescriptions of both MMI/CMZ and PTU (n = 4178). Individuals treated with ATDs were more often women and tended to be older than the nonexposed group (Table 1).

Table 1. Characteristics of Individuals in the Danish Population and in the Study Population on January 1, 2003

		The Study Population	
	The Danish Population[a]	No ATD Treatment January 1, 1995, Through September 30, 2010	ATD Treatment January 1, 1995, Through September 30, 2010
Individuals, n	5 383 507	2 270 954	28 998
Gender, n (%)			
Female	2 721 084 (50.5)	1 139 312 (50.2)	23 729 (81.8)
Male	2 662 423 (49.5)	1 131 642 (49.8)	5269 (18.2)
Age, y, mean (SD)[b]	39	42 (11.4)	45 (10.9)
Age, y, n (%)			
<20	1 299 812 (24.1)	25 157 (1.1)	117 (0.4)
20–29	673 685 (12.5)	330 664 (14.6)	2463 (8.5)
30–39	816 853 (15.2)	648 041 (28.5)	6356 (21.9)
40–49	752 029 (14.0)	610 992 (26.9)	8410 (29.0)
50–59	757 233 (14.1)	526 946 (23.2)	9214 (31.8)
≥60	866 906 (16.1)	129 154 (5.7)	2438 (8.4)
Origin, n (%)[c]			
Born in Denmark	4 979 318 (92.5)	2 076 249 (92.1)	26 673 (92.4)
Not born in Denmark	404 189 (7.5)	176 997 (7.9)	2199 (7.6)

The study population was further stratified by redeemed prescription(s) of ATDs.

[a] Data for the Danish population were obtained from Statistic Denmark.

[b] Information on SD was not available for the Danish population.

[c] Individuals in the study population with missing information on origin (n = 17 834) were not included.

Among all ATDs exposed, 45 cases of ATD-associated agranulocytosis and 10 cases of ATD-associated liver failure were identified (Figure 1) in 53 individuals (two individuals were diagnosed with both agranulocytosis and liver failure). For both types of side effects, there was a female predominance (Table 2) in line with the more frequent use of ATD among women. ATD-associated agranulocytosis and liver failure both developed at an earlier age compared with cases not associated with the use of ATDs (Table 2). Looking into details on the ATD-associated events, 36 developed during treatment with MMI and 19 during treatment with PTU (Table 3). Thus, MMI-asociated side effects were twice as frequent in the study population, but this should be considered in relation to the almost 5 times more frequent use of MMI than PTU. When stratified by type of ATD, the frequency of agranulocytosis was higher among individuals treated with PTU (0.27%) than with MMI/CMZ (0.11%, $P = .02$). Among PTU exposed, a group of 3231 individuals were treated with MMI before PTU. The frequency of agranulocytosis in this group (0.28%) was not significantly different from the frequency in individuals who primarily were treated with PTU (0.26%, $P = 1.0$). The frequency of liver failure was similar among individuals treated with PTU (0.05%) and MMI/CMZ (0.03%, $P = .4$). All cases of PTU-associated liver failure (n = 3) developed in individuals who were treated with MMI/CMZ before PTU.

Among the 53 individuals identified with side effects, 40 (75.5%) developed the side effect during their first-time treatment with ATD, whereas 13 (24.5%) had the event during treatment for hyperthyroidism relapse (Table 3). The majority developed the side effect during their first hyperthyroidism relapse, but four individuals developed agranulocytosis during a second or later relapse of hyperthyroidism. The time interval from the end of the prior treatment to the initiation of the relapse treatment was a median of 3.3 years.

Overall, the vast majority of side effects developed within 3 months after current ATD treatment (first time or relapse) had been initiated (Figure 2). All cases were hospitalized and changes in therapy were performed (Table 3). A total of four individuals died in relation to the side effect.

In our entire study population, ATD-associated agranulocytosis was considerably more frequent than liver failure, which was also the case after standardization to the entire Danish population (Table 4). To specifically evaluate the frequency of agranulocytosis and liver failure associated with the use of ATDs in pregnancy, the study population was restricted to women (n = 517 163) who gave birth to a live-born child from 1996 through 2008 (n = 830 680 pregnancies). In 2115 pregnancies, the mother redeemed prescriptions of ATDs (MMI/CMZ, n = 1347; PTU, n = 1103, including a group of pregnancies with usage of both MMI/CMZ and PTU [n = 335]). One case of agranulocytosis and one case of liver failure in pregnancy were observed (Table 4), both during treatment with PTU. Overall, ATD-associated agranulocytosis and

Table 2. Characteristics of Cases of Agranulocytosis and Liver Failure Stratified by ATD Treatment

		ATD Treatment	
	No ATD Treatment	**Event Not Associated With ATD**	**Event Potentially Associated With ATD**
Agranulocytosis, n	2978	72	45
Gender, n (%)			
Female	1609 (54.0)	55 (76.4)	38 (84.4)
Male	1369 (46.0)	17 (23.6)	7 (15.6)
Age, y, mean (SD)[a]	50 (11.9)	49 (11.4)	43 (10.5)
Age, y, n (%)[a]			
<20	15 (0.5)	1 (1.4)	0 (0)
20–29	137 (4.6)	3 (4.2)	3 (6.7)
30–39	456 (15.3)	12 (16.7)	18 (40.0)
40–49	762 (25.6)	23 (31.9)	10 (22.2)
50–59	922 (31.0)	19 (26.4)	12 (26.7)
≥60	686 (23.0)	14 (19.4)	2 (4.4)
Origin, n (%)[b]			
Born in Denmark	2766 (93.5)	64 (90.1)	42 (93.3)
Not born in Denmark	194 (6.5)	7 (9.9)	3 (6.7)
Liver failure, n	5227	64	10
Gender, n (%)			
Female	2307 (44.1)	50 (78.1)	6 (60.0)
Male	2920 (55.9)	14 (21.9)	4 (40.0)
Age, y, mean (SD)[a]	50 (11.1)	50 (11.5)	44 (15.1)
Age, y, n (%)[a]			
<20	68 (1.3)	0 (0)	0 (0)
20–29	243 (4.7)	5 (7.8)	1 (10.0)
30–39	596 (11.4)	7 (10.9)	4 (40.0)
40–49	1466 (28.0)	17 (26.6)	2 (20.0)
50–59	1961 (37.5)	21 (32.8)	2 (20.0)
≥60	893 (17.1)	14 (21.9)	1 (10.0)
Origin, n (%)[c]			
Born in Denmark	4865 (93.6)	60 (93.8)	9 (90.0)
Not born in Denmark	330 (6.4)	4 (6.2)	1 (10.0)

Cases among ATD-treated individuals were grouped according to whether the event was associated with the use of ATDs.

[a] Age in years at the diagnosis of the event.

[b] Individuals with missing information on origin (n = 19) were not included.

[c] Individuals with missing information on origin (n = 32) were not included.

liver failure were less frequently observed in pregnant women than in the general population (Table 4).

The 830 680 pregnancies terminated with the live birth of 848 022 children of whom 2206 had been exposed to maternal use of ATDs in the pregnancy. As explained in detail in the Supplemental Materials and Methods, altogether 75 children were estimated to have birth defects associated with the maternal use of ATDs in the pregnancy (Table 4). Compared with the frequency of ATD-associated agranulocytosis and liver failure in the population in general, birth defects and agranulocytosis had similar frequencies and were more common than liver failure (Table 4). For the use of ATD in pregnant women, birth defects were much more frequent than both agranulocytosis and liver failure (Table 4).

Discussion

In a Danish nationwide cohort, severe side effects to the use of ATDs for the treatment of hyperthyroidism were uncommon, with an estimated 44 cases of birth defects, 41 cases of agranulocytosis, and 11 cases of liver failure associated with the use of ATD during a 10-year period in a population of 5 million inhabitants. For the use of ATD in pregnancy, agranulocytosis and liver failure were both rare, with less than one case of each of these side effects in pregnant women during a 10-year period in a population of 5 million inhabitants, but as opposed to this, 44 live-born children would have birth defects associated with the maternal use of ATDs in the pregnancy.

ATDs have been used for the treatment of hyperthyroidism for decades, and it is in many countries the treatment of choice in patients with hyperthyroidism caused by Graves' disease (8). ATDs are easy to use, and in contrast to definitive treatments (radioiodine and surgery), the drugs induce no damage to the thyroid gland (8). However, similar to many other types of drug therapy, adverse side effects to the use of ATDs have been described. Considering this, it is important to distinguish between the

Table 3. Characteristics of 55 ATD-Associated Agranulocytosis and Liver Failure Events in 53 Individuals

	Agranulocytosis[a] (n = 45)	Liver Failure[a] (n = 10)
Type of ATD causing the event, n (%)		
MMI[b]	29 (64.4)	7 (70.0)
PTU[c]	16 (35.6)	3 (30.0)
Duration of ATD treatment up to the event, d, median (IQR[d])	36 (26–58)	49 (30–127)
MMI	36 (27–51)	42 (27–54)
PTU	38 (20–251)	159 (116–203)
Current ATD treatment, n (%)		
First-time ATD treatment	33 (73.3)	7 (70.0)
ATD treatment for hyperthyroidism relapse	12 (26.7)	3 (30.0)
Duration of hospitalization at event, d, median (IQR[d])	7 (5–13)	7 (5–30)
MMI	8 (5–13)	6 (5–24)
PTU	6 (4–12)	30 (3–38)
Consequence of event		
Death[e]	4 (8.9)	1 (10.0)
No further ATD treatment	4 (8.9)	0 (0.0)
Change to another ATD	15 (33.3)	4 (40.0)
Total thyroidectomy	7 (15.6)	3 (30.0)
Radioiodine[f]	15 (33.3)	2 (20.0)

Abbreviation: IQR, interquartile range.

[a] Two individuals were diagnosed with both agranulocytosis and liver failure and were included in both groups.

[b] Carbimazole (n = 1); PTU before MMI treatment (n = 2).

[c] MMI before PTU treatment (n = 12).

[d] IQR (25th to 75th percentile), except for PTU-associated liver failure (n = 3), which is a range (minimum-maximum).

[e] A total of four individuals died; one individual had a diagnosis of both agranulocytosis and liver failure. Case summaries are as follows: 37-year-old female with agranulocytosis and liver failure after 42 days of MMI treatment for hyperthyroidism relapse; 63-year-old female with agranulocytosis after 38 days of first-time MMI treatment; 42-year-old female with agranulocytosis after 56 days of first-time PTU treatment; 55-year-old female with agranulocytosis after 82 days of PTU treatment for hyperthyroidism relapse.

[f] Defined by subsequent redeemed prescriptions of L-T4 with no registration of thyroid surgery.

type and severity of side effects. Minor reactions to the use of ATDs have been reported in up to 5%–10% of patients, and most commonly these are cutaneous reactions that are typically dose dependent (8). On the other hand, major side effects are considered rare but important to recognize because they are potentially life threatening. Such major reactions can present in many ways (vasculitis, arthritis, pancreatitis), but the most common serious side effect is blood dyscrasias, particularly agranulocytosis (8).

The frequency of ATD-associated agranulocytosis has been reported in the range from 0.1% to 0.5% in retrospective studies from Japan with review of medical records from a large number of individuals treated with ATDs for the hyperthyroidism of Graves' disease (15–18). These figures are in line with the frequency of ATD-associated agranulocytosis observed in the present study (0.16%). Furthermore, similarities are to be noted between our and previous findings including the tendency for agranulocytosis to develop within 3 months after the initiation of treatment or relapse treatment and to be nonfatal in most cases (15–20).

We observed that agranulocytosis was more frequent during treatment with PTU than MMI/CMZ. In Denmark, MMI/CMZ is the most commonly used ATD for first-time treatment of hyperthyroidism, whereas PTU is typically used in individuals who do not tolerate MMI/CMZ, in severe hyperthyroidism, and in pregnant women. Considering this, it could be speculated if individuals receiving PTU are in general more prone to develop side effects, eg, they receive PTU because they did not tolerate MMI/CMZ. Our data did, however, not support this hypothesis because we found similar frequencies of agranulocytosis among individuals who were treated with PTU after the previous use of MMI and those who were treated only with PTU. Other authors have reported a similar frequency of agranulocytosis associated with MMI and PTU (15).

Another major and serious side effect to the use of ATDs is liver failure (8). The finding that PTU was the third most common cause of drug-related liver transplantation in the United States and that one-third of the registered cases were children and adolescents has been much discussed in the literature and in clinical guidelines on the management of hyperthyroidism (9, 10). Both PTU and MMI/CMZ have been associated with liver abnormalities, but whereas PTU may induce hepatocullular injury that can be fatal, the abnormalities associated with MMI/CMZ appear to be more of a cholestatic process (21). Estimates

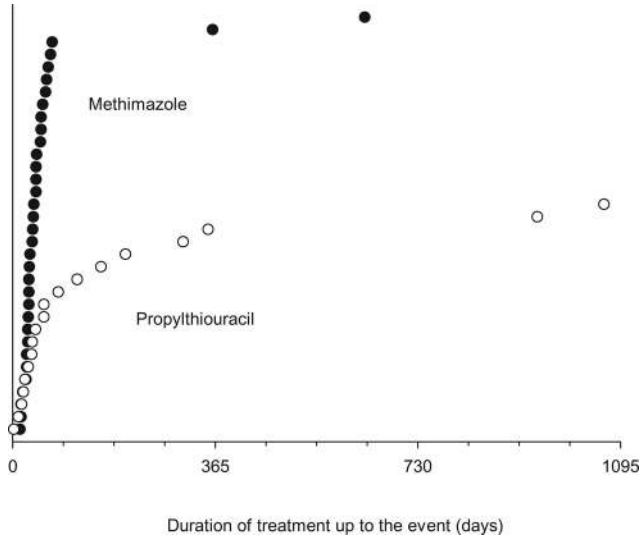

Figure 2. Duration in days of the most recent ATD treatment up to the event for the cases of ATD-associated agranulocytosis and liver failure. Cases of liver failure (n = 10) developed after 24, 27, 31, 42, 43, 54, and 68 days of MMI treatment and 116, 159, and 203 days of PTU treatment. Two individuals were diagnosed with both agranulocytosis and liver failure after 27 and 42 days of treatment with MMI and were illustrated only once.

on the frequency of liver side effects to the use of ATD are uncertain due to the wide spectrum of liver abnormalities recorded and may range up to 1% (21–23). In our study, 0.03% of ATD-exposed individuals developed liver failure and one case diagnosed after 42 days of MMI treatment was fatal. We observed no difference in the frequency of liver failure among individuals treated with MMI and PTU, which seems to be in line with a recent study from China (23), but the overall frequency of ATD-associated liver failure was higher in the Chinese study (1.0%) than in our study. Notably, the Chinese study included 8864 patients who were selected for radioiodine therapy. One cause of this selection might have been a side effect to the use of ATD.

Approximately one in four of the events that we observed developed during treatment for hyperthyroidism relapse. In Denmark, it is common clinical practice to give a second course of ATD for the treatment of hyperthyroidism relapse, and our results suggest that the frequency of severe side effects is of the same magnitude during re-exposure, eg, if it is hypothesized that one-third of ATD-treated individuals would also be treated with an ATD for hyperthyroidism relapse, the frequency of developing severe side effects to the use of ATD would be similar during first-time treatment and relapse treatment. Importantly, our data stress the necessity of clinical awareness on severe side effects both when an ATD is used for first-time treatment and for the treatment of relapse.

All the cases of side effects that we describe were hospitalized and the specific ATD was withdrawn. Notably, approximately one-third of the patients were switched to another ATD after they were diagnosed with agranulocytosis or liver failure. The type of data used for the present study does not allow a conclusion on the reason for this clinical behavior. It may be speculated that the responsible physician regarded the risk from hyperthyroidism relapse more severe that the risk of side effects to the other drug. In some cases, the second drug was used only until thyroid surgery was performed. None of the cases had a registration of severe side effects during the subsequent treatment with another ATD.

ATD is the treatment of choice for hyperthyroidism in pregnancy (3–5) and is also in general a commonly used treatment in patients with Graves' disease, implying that

Table 4. Cases of Agranulocytosis, Liver Failure, and Birth Defects Associated With the Use of ATD in the General Population and in Pregnancy

	Agranulocytosis, n	Liver Failure, n	Birth Defects, n
In the general population			
Cases in the Danish population[a]	70	19	
Cases per 5 million inhabitants per 10 y	41	11	
Cases per 10 000 ATD exposed	16	3	
In pregnant women			
Cases in the Danish population	1[b]	1[c]	75
Cases per 5 million inhabitants per 10 y	0.6	0.6	44
Cases/10 000 ATD exposed	5	5	340

[a] Cases observed in the study population (1995–2010) standardized to the age distribution of the Danish population on January 1, 2003 (5 383 507).

[b] Case summary is as follows: 20 year old, expecting her second child, first time diagnosed and treated with PTU in gestational week 15, hospitalized with agranulocytosis in gestational week 22 (2 d of hospitalization), no further treatment of maternal hyperthyroidism in or after the pregnancy, and vaginal delivery of a live-born child at term.

[c] Case summary is as follows: 22 year old, expecting her first child, 3 years earlier treated with MMI in a 4-year period, relapse and initiation of MMI treatment 4 months before getting pregnant, shift to PTU 2 months before getting pregnant and continued this treatment in the early pregnancy, hospitalized with liver failure in gestational week 10 (5 wk of hospitalization in specialist unit), no further treatment of maternal hyperthyroidism in the pregnancy, vaginal delivery of a live-born child at term, total thyroidectomy 4 months after birth of the child.

female patients often receive ATDs at the time they become pregnant (24, 25). Concern on the possibility of birth defects associated with the use of ATD in pregnancy was initially brought forward in 1972 (6). After this time, emerging evidence has linked the use of MMI and CMZ in the first trimester of pregnancy with aplasia cutis and other severe side effects such as upper airway and gut atresias, abdominal wall defects, and malformations of the eyes, the urinary tract, and the heart (2, 26–28). More recent evidence has shown that also the use of PTU in early pregnancy is associated with an increased risk of birth defects, which, however, include other types of malformations that appear less serious (sinus/cyst in the face and neck region and malformations of the urinary system) (2, 7). Thus, current guidelines recommend the use of PTU in early pregnancy, considering the risk of birth defects and the shift from PTU to MMI/CMZ after the first trimester of pregnancy to reduce the risk of liver failure associated with PTU (3–5). In Japan, fear of MMI-associated birth defects has led to a common use of iodine for the treatment of Graves' disease in early pregnancy (29, 30).

We studied the frequency of birth defects, agranulocytosis, and liver failure associated with the use of ATDs in a large, nationwide cohort. Children and elderly people were underrepresented in the study population, but standardization to the size and age distribution of entire Danish population was performed. The validity and coverage of the information in the Danish nationwide registers are considered to be high (11–14), but it should be stressed that this type of information is only an indicator of exposure, and we do not know whether the patient actually used the medicine. Cases of ATD-associated agranulocytosis and liver failure were identified from an individual review of registrations, which was made possible from the close relationship between exposure and outcome in a patient. The method applied for the evaluation of ATD-associated birth defects was different due to the time difference between exposure in pregnancy and outcome diagnosis after birth of the child, making individual assessment uncertain. The conditioning on live births was necessary to evaluate birth defects but could introduce fetal survival bias.

Our data indicate that the major burden of side effects to the use of ATDs in pregnancy is birth defects and that both agranulocytosis and also liver failure are rare in pregnant women. This is in line with other reports (31–33). An important consideration is that thyroid hormones are essential developmental factors and crucial in the regulation of fetal brain development (34, 35). Both maternal hyperthyroidism and hypothyroidism, and especially untreated or inadequately treated disease, are associated with pregnancy complications and may even program the fetus to the later development of disease (36–38). Thus, the management of hyperthyroidism in pregnancy must be focused on keeping the mother and fetus euthyroid and also on reducing the risk of birth defects associated with the use of ATDs. On the other hand, the risk of ATD-induced agranulocytosis and liver failure in pregnancy is comparatively low and therefore not a primary concern.

Conclusion

MMI/CMZ has a better pharmacokinetic profile, and it is the preferred ATD in nonpregnant individuals and particularly in children considering the risk of liver failure associated with PTU (8–10). For the use of ATDs in pregnant women, the dominating side effect is birth defects. The risk of agranulocytosis and liver failure should be kept in mind, but it is less important.

Clinical attention to restrict the use of ATDs in the teratogenic period of early pregnancy whenever possible (27) seems most crucial in reducing the burden of side effects to the use of ATDs in a population. One option to restrict such use of ATDs is to advocate ablative therapy (surgical total thyroidectomy or radioiodine) before the woman becomes pregnant. This option may be appropriate in women with severe Graves' disease that is difficult to control. If ATD therapy is chosen in women who may become pregnant, focus should be on the early detection of pregnancy, optimally the latest in gestational week 5. When pregnancy is detected, one possibility is to shift therapy from MMI to PTU because PTU-associated birth defects seem less severe (2). Another possibility in women who are considered in remission of Graves' disease is to withdraw ATDs in the early pregnancy period and to perform weekly thyroid function tests during the first trimester of pregnancy to detect and correct any relapse of hyperthyroidism at an early stage (27).

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