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Side Effects of Anti-Thyroid Drugs and Their Impact on the Choice of Treatment for Thyrotoxicosis in Pregnancy

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Key Words

Thyroid · Pregnancy · Carbimazole · Methimazole · Propylthiouracil · Thionamide · Embryopathy · Congenital malformation · Hepatotoxicity · Agranulocytosis

Abstract

Introduction: Hyperthyroidism in pregnancy is a serious condition and its management is complex. Whilst carbimazole/methimazole (CBZ/MMI) and propylthiouracil (PTU) have similar efficacies in controlling hyperthyroidism, their risk of side effects such as major congenital abnormalities and hepatotoxicity are different. ***Methods:*** Various combinations of the terms 'anti-thyroid drugs', 'thionamide', 'carbimazole', 'methimazole', 'propylthiouracil', 'pregnancy', 'side effects', 'agranulocytosis', 'birth defects', 'congenital malformations', 'embryopathy', 'aplasia cutis', 'hepatotoxicity', 'hepatic failure', 'maternal' and 'fetus' were used to search MEDLINE and the Cochrane library. The references of retrieved papers were also reviewed. ***Results:*** There is increasing evidence for a CBZ/MMI embryopathy, whilst data remain lacking for major congenital abnormalities with PTU. In contrast, PTU is associated with increased risk of severe liver injury. Management strategies to reduce these risks by using PTU in the first trimester and CBZ/MMI in the later trimesters remain untested. ***Conclusion:*** More evidence is still needed in defining the relative risks between CBZ/MMI and PTU of major congenital abnormalities and severe liver injury in pregnancy. Studies are also needed to establish the suitability of recent management suggestions in switching from PTU to CBZ/MMI after the first trimester. Major adverse outcomes secondary to CBZ/MMI and PTU are rare, and inadequately treated hyperthyroidism poses a far greater risk.

Introduction

Hyperthyroidism in pregnancy is a serious condition, resulting in increased risk of adverse obstetric outcomes including miscarriage, stillbirth, pre-term birth and intra-uterine growth restriction [1]. Its management is complex, and currently a key debate amongst endocrinologists. Anti-thyroid drugs (ATDs) have been used since the 1940s, and are the preferred treatment during pregnancy. Radio-iodine is absolutely contraindicated [2, 3], and thyroidectomy in pregnancy carries increased morbidity compared to non-pregnant women [4] and may also result in increased risk of subsequent fetal thyrotoxicosis [5].

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A recent Cochrane review failed to identify any randomised controlled trial comparing ATD interventions in pregnant women with hyperthyroidism [6]. However, carbimazole (CBZ), its active metabolite, methimazole (MMI) and propylthiouracil (PTU) are all thought to be equally effective in controlling hyperthyroidism [7]. Therefore, the choice of ATD is not based on their relative treatment efficacy, but instead on consideration of side effects and risk of profound clinical consequences, in particular teratogenicity and serious liver injury. The objective of this review is to examine these relevant considerations when selecting which ATD to use in pregnancy and in those planning pregnancy.

Search Strategy

Various combinations of 'anti-thyroid drugs', 'thionamide', 'carbimazole', 'methimazole', 'propylthiouracil', 'pregnancy', 'side effects', 'agranulocytosis', 'birth defects', 'congenital malformations', 'embryopathy', 'aplasia cutis', 'hepatotoxicity', 'hepatic failure' both separately and in conjunction with the terms 'maternal' and 'fetus' were used to search MEDLINE and the Cochrane library. The references of retrieved papers were also reviewed. Only English language papers were studied.

Results

Frequency and Consequences of Hyperthyroidism in Pregnancy

The prevalence of hyperthyroidism in pregnancy is between 0.1 and 1% [1, 8, 9], and if untreated or inadequately treated, there is an increased risk of obstetric complications and fetal loss [1, 10]. Furthermore, women with the poorest control of the hyperthyroidism during pregnancy have the highest rate of complications [11]. For example, in women receiving ATD treatment for hyperthyroidism during pregnancy, the odds ratio for having a low-birthweight (<2,500 g) infant was 2.4 (95% CI 1.4–4.1), rising to 9.2 (95% CI 5.5–16) in untreated women, and the odds of premature delivery were 2.78 (95% CI 0.33–23.5) in those receiving ATD treatment but 16.5 (95% CI 2.09–130) in untreated women [12]. It is however unclear why women in this sample were untreated, and a proportion of this negative impact may reflect other confounding factors such as lower socioeconomic status, lower health-seeking behaviour or access to medical care.

Maternal ATD Use and Teratogenicity

Placental Transfer of ATDs

All ATDs cross the placenta, and therefore the lowest possible dose to control hyperthyroidism is recommended [1]. From the totality of the available evidence, it is still unclear whether there is a substantial difference in placental transfer between CBZ/MMI and PTU.

The only in vivo study to date demonstrated that PTU was transferred across placenta less than CBZ/MMI; however, this was a small study with only 7 women having complete data [13]. In this report, pregnant women ingested ^{35}S-labeled ATDs 2 h before the elective termination of pregnancies that ranged in gestational age from 8 to 20 weeks. For CBZ/MMI (n = 5), the ratio of fetal cord blood CBZ/MMI levels to maternal drug levels ranged from 0.72 to 1 indicating a high rate of drug transfer, whereas for PTU (n = 2), the ratio ranged from 0.27 to 0.35 indicating a substantially lower transfer rate. In addition, the investigators obtained drug transfer data from pregnant rats that also supported these observations [13].

Although PTU is more tightly bound to serum albumin than CBZ/MMI and therefore theoretically may pass less through the placenta, it appears that transfer across the placenta is not entirely protein dependent, and there is some evidence from in vitro studies that transfer of CBZ/MMI and PTU is very similar in at-term placentas [14]. Furthermore, cord PTU levels were found to be higher than maternal concentrations in patients treated with PTU until term [15]. There were also no identified differences in thyroid hormone and TSH concentrations in cord blood at birth between patients treated with CBZ/MMI and PTU [16], although this study was underpowered to detect modest differences.

At present, it appears likely that CBZ/MMI and PTU have comparable transfer across the placenta in the later stages of pregnancy. It is still unclear whether CBZ/MMI crosses the placenta more freely than PTU in the first trimester, with subsequent increased potential for teratogenicity.

ATDs and Risk of Teratogenicity

The role of ATDs in causing teratogenicity has been controversial as hyperthyroidism itself can cause congenital abnormalities in particular cardiac and renal abnormalities [17]. One study (n = 643) reported more birth defects in hyperthyroid patients (6% untreated vs. 1.7% treated) in comparison to euthyroid controls (0%) [18]. A more recent study identified that developmental dysplasia of the hip was associated with hyperthyroidism in the first trimester secondary to Graves' disease and severe

hyperemesis gravidarum ($p < 0.0001$, for both) [19]. In contrast, it has been recently highlighted that the overall rate of congenital malformations is not related to maternal thyroid status in the first trimester [20]. Furthermore, a US study identified that the rate of congenital malformations in babies born to women who were hyperthyroid during the first trimester was 3% (3 of 99), very similar to the rate of fetal malformations in controls (3%, 6 of 185) [21].

Scalp defects due to congenital aplasia cutis in babies exposed to MMI in the first trimester were observed as long ago as 1972 [22]. Whilst aplasia cutis can be familial or occur spontaneously, it is rare in babies not exposed to teratogens, with a birth prevalence of 0.03% [23]. In keeping with this, there was circumstantial evidence of an association between MMI and aplasia cutis following reports of increased incidence of aplasia cutis in some parts of Spain in the late 1980s thought to be due to illegal use of MMI in animal feed [24]. Whilst initial reports were of only an increased incidence of scalp defects in the infants of CBZ/MMI-treated mothers in pregnancy, many other more serious anomalies have now been described including choanal atresia, tracheo-oesophageal fistula, gastrointestinal anomalies in particular oesophageal atresia and patent vitellointestinal duct, omphalocele, athelia/hypothelia, developmental delay, hearing loss, and dysmorphic facial features giving rise to the CBZ embryopathy phenotype [25–28].

The identification of several otherwise rare defects together in children exposed to CBZ/MMI, but not to PTU, in utero supports the concept of an embryopathy that is specific to CBZ/MMI. Interestingly, a recent review of 31 published cases of CBZ/MMI embryopathy has shown that the embryopathy does not appear to be related to the dose of drug or maternal thyroid status [27]. There is also high perinatal mortality and premature births associated with this embryopathy [27].

CBZ/MMI has historically been more widely used than PTU in many parts of the world including Europe; MMI has also been used more preferentially in the USA since the mid 1990s [29]. This could have resulted in a reporting bias of individual cases of congenital abnormalities for CBZ/MMI. Fortunately, several cohort and large retrospective case-control studies are available which limit this bias. In particular, the large case-control studies by Clementi et al. [30] (n = 18,000) and Yoshihara et al. [31] (n = 5,069) provide the most compelling evidence of an association between CBZ/MMI and major congenital abnormalities. A summary of the important case-control and cohort studies is shown in table 1. Two small cohort studies failed to find any difference in the number of major congenital abnormalities between CBZ/MMI and PTU and PTU vs. control [21, 32] although this may be due to lack of power. Analysis of birth registry data in Sweden found 4 reports between 1995 and 2000 of infants born with oesophageal atresia and omphalocele or choanal atresia, 3 of whom had been exposed to MMI in the first trimester; there was no association between these anomalies and PTU [33]. A recent large case-control study [30] which included over 18,000 cases with congenital malformations, of which 127 were exposed to ATD in the first trimester confirmed the possible link identified between CBZ and choanal atresia and omphalocele ($p < 0.01$) which had been identified in smaller studies [25–28, 34]. In addition, this paper demonstrated a potential association between PTU and situs inversus with/without dextrocardia, other cardiac outflow tract defects and unilateral renal agenesis/dysgenesis. However, this was based on a small number of cases, and more research is still needed in this area.

A recent Japanese study of fetal outcomes of ATD treatment in the first trimester of pregnancy in women with Graves' disease had similar outcomes [31]. In this report, fetal outcomes were available in 1,426 pregnancies exposed to MMI alone in the first trimester, in 1,578 outcomes in pregnancies exposed to PTU alone and data were available on 2,065 women who had received no medication for the treatment of Graves' disease during the first trimester (control group). The overall rate of major anomalies in the MMI group was 4.1% (50 of 1,231), and it was significantly higher than the 2.1% (40 of 1,906) in the control group ($p = 0.002$). In particular, exposure to MMI in the first trimester was significantly associated with the birth of an infant with aplasia cutis congenita, omphalocele, and omphalomesenteric duct anomaly ($p < 0.0001$, $p = 0.0013$, $p = 0.0001$, respectively). The overall rate of major anomalies in the PTU group was 1.9% (21 of 1,399), which was similar to the control group ($p = 0.709$). Another prospective controlled cohort study of 115 PTU-exposed pregnancies and 1,141 controls also observed comparable rates of major anomalies in the two groups (1.3% vs. 3.2%, respectively; $p = 0.507$) [32]; however, no comparison was made with CBZ/MMI.

Overall, the evidence for an association between CBZ/MMI and congenital malformations is strengthening on the basis of repeated typical presentations and increasing evidence from both cohort and case-control studies. Furthermore, there is still higher reporting of birth defects with CBZ than PTU to the UK pharmacovigilance agency in recent years despite the increase in PTU use in preg-

Table 1. Case-control and cohort studies of major congenital abnormalities following exposure to ATD in utero

Report	Country	Study type	Agent studied	Key outcomes
Momotani et al. [18]	Japan	Prospective study of 643 neonates divided into 4 groups depending on MMI exposure and maternal thyroid status during the first trimester	MMI	Highest incidence of congenital malformations was in untreated women with hyperthyroidism ($p < 0.01$)
Di Gianantonio et al. [69]	Italy	Prospective study of 241 women counselled by the European teratology information services because of exposure to MMI; 1,098 controls	MMI	No increase in the general rate of major congenital abnormalities between MMI and control, but two cases were identified that indicated choanal as well as oesophageal atresia may have a higher incidence in newborns exposed to MMI
Karlsson et al. [33]	Sweden	Cohort (Swedish birth registry, 1995–2000)	MMI and PTU	4 reports of infants born with oesophageal atresia and omphalocele or choanal atresia, 3 of whom had been exposed to MMI in the first trimester. No association between these anomalies and PTU
Wing et al. [21]	USA	Retrospective case review of 185 hyperthyroid patients; 99 patients treated with PTU and 36 with MMI	MMI and PTU	No significant difference in congenital abnormalities (2.7% MMI, 3.0% PTU)
Barbero et al. [70]	Argentina	Multi-centre case control (61 cases of choanal atresia, 183 controls)	MMI	Odds ratio for choanal atresia if exposed to MMI = 17.75 (95% CI 3.49–121.40)
Rosenfeld et al. [32]	Israel	Prospective observational controlled cohort study of 115 PTU-exposed pregnancies of women counselled by the Israeli Teratology Information Service; 1,141 controls	PTU	Rate of major anomalies was comparable between the PTU group (1.3%), and control (3.2%), $p = 0.51$
Clementi et al. [30]	Italy	Case-control study of over 18,000 congenital abnormalities; of these, 127 exposed to ATD in the first trimester	CBZ/MMI and PTU	Significant association between exposure to CBZ/MMI and choanal atresia and omphalocele ($p < 0.01$). Potential link between PTU and cardiac defects
Koening et al. [71]	France	Retrospective analysis (Nice Pharmacovigilance Department)	MMI	6 cases of MMI embryopathy, no cases reported with PTU
Bowman and Vaidya [35]	UK	Analysis of all birth defects related to maternal treatment with CBZ or PTU reported over a 47-year period via the Yellow Card Scheme	CBZ and PTU	57 cases with 97 anomalies were reported following in utero exposure to CBZ. These anomalies included aplasia cutis, choanal atresia, tracheo-oesophageal fistula, and patent vitellointestinal duct. Only 6 cases with 11 anomalies were reported for PTU, all within the last 15 years
Chen et al. [72]	China	Matched case-control study: 2,830 pregnant women with hyperthyroidism (2,127 not on ATD, 703 on ATD); 14,150 age-matched controls	MMI and PTU	No difference in major congenital abnormalities in children born to hyperthyroid women not on ATD (0.71%), hyperthyroid women on ATD (0.71%) and controls (0.65%)
Yoshihara et al. [31]	Japan	Retrospective case control study: 1,426 pregnancies exposed to MMI in the first trimester, 1,578 pregnancies exposed to PTU alone in the first trimester, 2,065 pregnancies who had received no medication for the treatment of Graves' disease during the first trimester were controls	MMI and PTU	More major congenital abnormalities with MMI ($p = 0.002$) compared to control. No difference in major congenital abnormalities with PTU compared to control

nancy [35]. However, the apparent lack of association between PTU and congenital malformations may still be because of historically lower use of the drug. Continued vigilance for congenital abnormalities secondary to PTU is still necessary as PTU was found to have higher teratogenic potential in murine embryos than MMI [36]. Furthermore, there has been a reported case of aplasia cutis secondary to PTU exposure during pregnancy and choanal atresia [37]. More recently, a case of aplasia cutis, with skin defect on both flanks, the thighs and the knees, but

Table 2. Reported cases of severe liver failure in pregnancy occurring secondary to PTU

Report	Country	Duration of PTU exposure (gestation)	Management	Maternal outcome	Fetal outcome
Parker [73]	Canada	6 months (20 weeks)	PTU discontinued; treated with MMI and propranolol	Recovered	Not described
Morris et al. [74]	USA	Unclear (25 weeks)	PTU discontinued; treated with MMI and propranolol; required liver transplant	Recovered	Growth retardation, premature, jaundice, fetal death
Kontoleon et al. [75]	Greece	Unclear	Cessation of PTU at 12 weeks; conversion to CBZ	Recovered	Uneventful
Ruiz et al. [76]	Chile	5 months (4 months)	Liver failure requiring ICU, initial recovery; however, subsequent miscarriage and recurrence of liver failure and death	Death	Death
Sequeira et al. [77]	Kenya/ USA	7 weeks (17 weeks)	Liver transplant at 18 weeks' gestation. Thyroidectomy	Recovered	MRI features suggestive of antenatal ischemic encephalopathy. Developmental delay
Taylor et al. [78]	UK	16 weeks (20 weeks)	Immediate cessation of PTU; started CBZ 3 weeks later. Transplant considered but not required	Recovered	Healthy baby at term

not on the scalp, was observed in an infant whose mother was exposed to PTU, but not CBZ/MMI in pregnancy [38].

ATDs and Severe Liver Injury

Hepatic side effects related to PTU are more common [39] and more severe, as compared to CBZ/MMI [40]. PTU is associated with a hepatitic pattern in contrast to predominantly cholestatic pattern with CBZ/MMI-related liver side effect. The risk of PTU and severe liver injury was highlighted in 2009 in following two meetings sponsored by the Eunice Kennedy Shriver National Institute of Child Health and Development and jointly by American Thyroid Association (ATA) and the US Food and Drug Administration (FDA), respectively [41]. The FDA Adverse Event Reporting System database, which was reviewed in the meetings, included 22 adults (9 fatal, 5 needing liver transplants) and 12 children (3 fatal, 6 needing liver transplants) with severe liver failure relating to PTU in the past two decades [41]. This led to the FDA issuing a black box warning for PTU in 2010 that notified healthcare professionals of these risks [42, 43].

Data from the United Network for Organ Sharing between October 1st 1987 and December 31st 2007 revealed that 661 patients (567 adults, 94 children) received a liver transplant for drug-induced acute liver failure in the United States [44]. In this report, PTU was identified as the cause of 2.9% (19/661) of all cases of drug-induced acute liver failure. It was the 4th leading cause of drug-induced liver failure (6%, 6/94) in children after paracetamol, valproic acid and isoniazid. Intriguingly, there were no reported cases of acute liver failure secondary to PTU in a large survey (n = 949) of acute liver failure in Scotland [45], suggesting that more data are needed to establish if certain groups of individuals are at greater risk.

Overall, the development of PTU-induced liver failure is likely to be idiosyncratic and difficult to predict, and no differences have been observed in age, PTU dose, or T_4 and T_3 levels at initial diagnosis between patients with and without hepatic injury [46, 47]. The high female preponderance (female:male 8.3:1) of PTU-induced liver failure [47] may simply reflect the higher incidence of thyrotoxicosis in women and subsequently higher use of PTU. In the absence of evidence showing a benefit, routine monitoring of liver function tests in pregnant women on PTU remains controversial [48]. Monitoring liver function tests may lead to increased anxiety, poor compliance and may not provide warning of the event. Furthermore, many patients on PTU develop raised liver enzymes; these levels tend to decrease or remain stable despite continuing the drug [49].

It should be highlighted that the development of severe liver injury in individuals on PTU is fortunately rare. It has been estimated that of around 4,000 pregnant women treated with PTU each year in the USA 4 will develop PTU-related severe liver injury [41]. It should also be noted that this assumption was based on general reporting of PTU-related hepatic complications and not pregnancy-specific data; therefore, this would not reflect the rate if it was higher in pregnancy. We found 6 reported cases of PTU-induced hepatitis during pregnancy in the medi-

Table 3. Reported cases of agranulocytosis secondary to antithyroid drugs during pregnancy and subsequent outcomes

Report	Country	Age (gestation)	Drug	Neutropaenia treatment	Definitive thyroid treatment (gestation)	Outcome
Davison et al. [79]	UK	31 (8 weeks)	PTU	spontaneous recovery	surgery (14 weeks)	healthy baby
Cho et al. [80]	Korea	28 (24 weeks)	PTU	spontaneous recovery	surgery (28 weeks)	healthy baby
Finucane et al. [81]	Ireland	31 (11 weeks)	PTU	spontaneous recovery	surgery (23 weeks)	healthy baby
Syed et al. [82]	UK	29 (3rd trimester)	PTU	spontaneous recovery	surgery (3rd trimester)	healthy baby
Murji et al. [83]	Canada	37 (3rd trimester)	PTU	spontaneous recovery	surgery (35 weeks)	healthy baby
Lim et al. [84]	Malaysia	33 (4 weeks)	CBZ	GCSF IV antibiotics	radio-iodine	termination of pregnancy

cal literature, summarised in table 2. From this small sample, it appears outcomes are particularly poor in pregnancy as there was 1 maternal death and 2 required liver transplant. Fetal outcomes were also poor, with 2 fetal deaths and 1 case of developmental delay in the 5 reported fetal outcomes. We also identified one case of neonatal hepatitis secondary to maternal treatment with PTU [50]. Clear guidance therefore needs to be routinely given to all healthcare professionals but in particular general practitioners and midwifes about the risk of PTU and severe liver injury, as they may be the first point of contact. They should be informed that early symptoms of liver failure such as itching, should not be attributed to pregnancy, but instead result in an urgent medical review as worse outcomes occur if there is delay in stopping PTU [51].

Risk of Agranulocytosis and Other Side Effects with ATDs

The most common side effects of ATDs are skin rashes, gastrointestinal symptoms such as nausea and vomiting, and altered taste (PTU). Agranulocytosis is a particularly feared complication; however, it is relatively rare in pregnancy as the risk may be higher in the elderly [52, 53] and lower doses are generally used in pregnancy. Table 3 shows case reports of agranulocytosis secondary to ATDs in pregnancy. Whilst most cases are secondary to PTU, this might reflect recent higher prescribing of PTU over CBZ/MMI in pregnancy.

The development of agranulocytosis should result in immediate cessation of the drug and full blood count monitoring with isolation and prophylactic antibiotics as indicated. Granulocyte colony-stimulating factor (GCSF) may shorten the time of recovery from agranulocytosis; however, to date no adequate and well-controlled studies regarding the use of the drug in pregnancy have been performed. A study has reported a possible relationship between abortion, fetal death, developmental anomalies, and placental embolism in pregnant rabbits given human GCSF [54]. Furthermore, there is evidence of trans-placental passage of GCSF in humans [55] although no major risk of congenital malformations has been reported in association with the drug. Therefore, GCSF should be used if potential benefit justifies the potential risk to the fetus (manufacturers' recommendation).

PTU has also been associated with the development of ANCA-positive vasculitis, and one case has occurred in pregnancy [56], requiring corticosteroids. A successful outcome was achieved in this case after switching to MMI.

Effects of Maternal ATD Treatment on the Fetal Thyroid

It has been known for a long time that both CBZ/MMI and PTU can cause fetal hypothyroidism and goitre [57]. As a result, the FDA has classified both CBZ/MMI and PTU as being of risk to the fetus [58]. A recent systematic review [59] also highlighted two cohort studies [16, 21] which reported on the prevalence of neonatal hypothyroidism in 133 hyperthyroid women treated with PTU compared with 79 hyperthyroid women treated with MMI. Meta-analysis of these studies revealed no difference between the two groups (RR = 1.50, 95% CI 0.58–3.88, p = 0.40). Overall, it appears for this outcome that the maintenance of appropriate maternal thyroid hormone levels is more important than the choice of ATD [60].

Physical and Mental Growth in Children Born to Mothers Treated with ATDs

Two studies have shown no differences in thyroid function or physical and psychomotor development be-

Table 4. Society recommendations regarding the use of anti-thyroid drugs in pregnancy

Authorities	Year	Recommendations
American College of Obstetrics and Gynecology [85]	2002	Either PTU or MMI can be used
British Thyroid Association, Association of Clinical Biochemists and British Thyroid Foundation [86]	2006	Patients on CBZ may be switched to PTU in pregnancy
American Thyroid Association and American Association of Clinical Endocrinologists [87]	2011	PTU in the first trimester; switch to MMI after the first trimester
American Thyroid Association [3]	2011	PTU in the first trimester; patients on MMI should switch to PTU if pregnancy confirmed in the first trimester; switch to MMI after the first trimester
The Endocrine Society [66]	2012	PTU should be used first line, if available particularly in the first trimester. If PTU is not tolerated can convert to MMI. As PTU is rarely associated with liver toxicity should change from PTU to MMI after the first trimester, with thyroid function testing 2 weeks after the transfer; also reasonable to monitor liver function tests every 2–4 weeks whilst on PTU

tween children born to CBZ/MMI or PTU treated hyperthyroid mothers during pregnancy and those born to euthyroid mothers [61, 62]. However, these studies were small and underpowered to detect even substantial differences. Again maintenance of appropriate maternal thyroid hormone levels is more important than the choice of ATD.

ATD Use after Pregnancy if Breastfeeding

This topic has been the subject of a recent excellent review in this journal [63]. In brief, CBZ/MMI are preferable due to the ongoing concerns of prolonged PTU exposure and risk of hepatotoxicity [3]. Whilst PTU may be less present in breast milk for an equivalent dose of CBZ/MMI [64], guidelines from the ATA recommend that maternal use of either MMI doses up to 20–30 mg/day or PTU doses up to 300 mg/day during lactation will not affect the infant's thyroid hormone levels significantly [3]. However, these guidelines also recommended that breastfeeding infants of mothers taking ATD should be screened with thyroid function tests and that patients should take their ATD dose just after breastfeeding, which should provide a 3- to 4-hour interval before they lactate again [3].

Current Management Strategies regarding the Use of ATDs in Pregnancy

A recent survey of members of the European Thyroid Association (ETA) highlighted that there was considerable variation in European practice in this field [65]. In particular, this survey showed inconsistencies in the treatment of women with Graves' disease planning pregnancy, the choice and monitoring of ATDs in pregnant women, and the choice of ATDs in lactating women. This disparity in the clinical practice also reflects the lack of evidence in this field and the need for further studies.

The main guidelines published by various learned societies regarding the use of ATDs in pregnancy are shown in table 4. The most recent guidelines from the ATA and the Endocrine Society recommend using PTU in the first trimester and CBZ/MMI afterwards [3, 66]. In theory, this should reduce the risk of congenital malformations secondary to CBZ/MMI as well as the risk of PTU associated severe liver injury by reducing PTU exposure. However, this approach has not been assessed in a well-designed study, and it is currently unknown if this is an effective or practical solution. These problems have been identified in a recent review [48] which highlighted that the optimal timing of any switch is currently unknown as completion of organogenesis does not occur until mid-gestation, close thyroid function monitoring will be required and most importantly there is no evidence that this will reduce PTU-induced hepatitis and CBZ/MMI-induced embryopathy.

There are also additional key limitations; for example, it is unclear if the consequences of changing medication will lead to dosage errors, or reduced compliance with subsequent adverse thyroid function, which may offset any advantages. Furthermore, it is still unclear whether this treatment regime would be appropriate in women

presenting at 10 weeks' gestation. Therefore, whilst we recommend the use of PTU in the first trimester, it is much less clear which patients should be transferred to CBZ/MMI after the first trimester. Any patients transferring from PTU to CBZ will need close monitoring of thyroid function every 2–4 weeks.

It is also unclear what the optimal strategy is for hyperthyroid women planning pregnancy. The recent ATA guidelines recommend using CBZ/MMI in women planning pregnancy and then convert to PTU only when pregnancy is confirmed [3]. However, given that patients may forget this advice and that there is often delay before the first antenatal visit, this approach increases the risk of exposure to CBZ/MMI between days 15–60 which are a critical time for organogenesis [67]. Therefore, in our view, for women planning pregnancy in the near future (where thyroidectomy or radio-iodine are not an option), PTU remains the preferred ATD.

Conclusion

This review has highlighted that the management of hyperthyroidism in pregnancy and in women planning pregnancy is complex and many issues still need addressing. In particular, data are lacking on whether there are key differences in placental transfer in the first trimester between CBZ/MMI and PTU, whether the apparent absence of association between PTU and congenital malformations is merely the reflection of lesser historical use of the drug as compared to CBZ/MMI, whether pregnant women have a different risk of PTU-induced hepatitis than the general population, whether it is practical to change from PTU in the first trimester to CBZ/MMI, and what is the optimum treatment for hyperthyroid women planning pregnancy.

Given the need for further data in this area, widespread standardised data collection in Europe may allow invaluable increased insight. Data regarding congenital abnormalities in pregnancies exposed to PTU, and any identified adverse outcomes such as relapse in hyperthyroidism with the relatively new practice of using PTU in the first trimester and CBZ/MMI afterwards would be particularly valuable. Having ETA members reporting pregnancy outcomes following treatment for hyperthyroidism could become a key future role of the ETA.

It should be highlighted that patients need to be managed sensitively and with firm reassurance as the risks of the more serious adverse outcomes such as embryopathy and severe liver injury are fortunately rare and poor compliance is more likely to lead to adverse outcomes. Given the complexity of the management of hyperthyroidism in pregnancy, introductory discussions should be had with all women of child-bearing age attending thyroid clinics [68] and as not all pregnancies are planned, all women with reproductive potential should be informed of the potential risk of teratogenicity when starting treatment with CBZ/MMI. It may be also worthwhile using definitive treatment such as radio-iodine or surgery if pregnancy is planned 12 months or so in the future.

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Disclosure Statement

The authors have no conflicts of interest to declare.

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