

MOTHERISK ROUNDS

The Safety of Methimazole and Propylthiouracil in Pregnancy: A Systematic Review

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Abstract

Background: Hyperthyroidism is one of the most common endocrine disorders in pregnant women, and it can severely complicate the course and outcome of pregnancy. Methimazole (MMI) and propylthiouracil (PTU) are the standard anti-thyroid drugs used in the treatment of hyperthyroidism in pregnancy. Traditionally, MMI has been considered to have clearer evidence of teratogenicity than PTU. Recent studies suggest that PTU can be hepatotoxic, leading to a United States Food and Drug Administration “black box alert.” We wished to systematically review the effects of PTU and MMI during pregnancy, and to compare maternal and fetal safety.

Methods: We conducted a systematic search of PubMed, EMBASE, TOXNET, TOXLINK, DART, Medscape, EBSCO, and Google. Both English and non-English publications were included. We excluded studies using anti-thyroid therapies other than PTU and MMI, studies not allowing interpretation of results, and abstracts of meetings.

Results: Overall, insufficient statistical power precluded determination of accurate rates of either MMI teratogenicity or PTU hepatotoxicity in cohort studies. However, a case–control study helped identify the relative risk of MMI-induced choanal atresia. A second case–control study failed to show that aplasia cutis congenita is associated with MMI. PTU has been associated with a rare but serious form of hepatic failure.

Conclusion: MMI causes a specific pattern of rare teratogenic effects after first trimester exposure, while PTU therapy may be followed by rare but severe hepatotoxic sequelae. It is therefore appropriate to use PTU to treat maternal hyperthyroidism during the first trimester of pregnancy, and to switch to MMI for the remainder of the pregnancy.

Résumé

Contexte : L'hyperthyroïdie est l'un des troubles endocriniens les plus courants chez les femmes enceintes et peut gravement compliquer l'évolution et l'issue de la grossesse. Le méthimazole (MMI) et le propylthiouracile (PTU) sont les antithyroïdiens standard qui sont utilisés dans la prise en charge de l'hyperthyroïdie pendant la grossesse. Traditionnellement, le MMI a été considéré comme présentant des signes de tératogénéicité plus manifestes que le PTU. Des études récentes laissent entendre que le PTU peut être hépatotoxique, ce qui a mené à la publication d'un encadré (« *black box alert* ») à ce sujet par la *Food and Drug Administration* américaine. Nous souhaitons procéder à l'analyse systématique des effets du PTU et du MMI pendant la grossesse, ainsi qu'à la comparaison de leur innocuité chez la mère et le fœtus.

Méthodes : Nous avons mené des recherches systématiques dans PubMed, EMBASE, TOXNET, TOXLINK, DART, Medscape, EBSCO et Google. Les documents publiés tant en anglais que dans d'autres langues ont été inclus. Nous avons exclu les études faisant appel à d'autres antithyroïdiens que le PTU et le MMI, les études ne permettant pas l'interprétation des résultats et les résumés de réunions.

Résultats : De façon globale, l'insuffisance de la puissance statistique a empêché la détermination de taux précis pour ce qui est de la tératogénéicité du MMI ou de l'hépatotoxicité du PTU dans les études de cohorte. Toutefois, une étude cas-témoins a contribué à identifier le risque relatif d'atrésie choanale attribuable au MMI. Une deuxième étude cas-témoins n'est pas parvenue à démontrer que l'aplasie ectodermique congénitale était associée au MMI. Le PTU a été associé à une forme rare mais grave d'insuffisance hépatique.

Conclusion : Le MMI cause un ensemble particulier d'effets tératogènes rares à la suite d'une exposition au cours du premier trimestre, tandis que le traitement au PTU peut donner lieu à des séquelles hépatotoxiques rares mais graves. Il s'avère donc approprié d'utiliser le PTU pour la prise en charge de l'hyperthyroïdie maternelle au cours du premier trimestre de la grossesse, pour ensuite passer au MMI pour le reste de la grossesse.

Key Words: Propylthiouracil, methimazole, birth defects, hyperthyroidism, pregnancy

Competing Interests: None declared.

INTRODUCTION

Hyperthyroidism is one of the most common endocrine disorders in pregnant women and can severely complicate the course and outcome of pregnancy. It is characterized by excessive secretion by the thyroid of tri-iodothyronine and thyroxine.¹ The most common cause of hyperthyroidism is Graves' disease, an organ-specific autoimmune disorder that is mediated by thyroid stimulatory immunoglobulins.² These autoantibodies mimic the action of thyroid stimulating hormone, leading to increased thyroid function. The diagnosis of hyperthyroidism is made when serum thyroid stimulating hormone is depressed and serum free T₄ and the free thyroxin index are elevated.³ Treatment options include anti-thyroid drugs, surgical resection of the thyroid, symptomatic relief (e.g., beta-blockers), and/or radiotherapy.⁴

In pregnant women, the incidence of hyperthyroidism is 0.2% to 0.3%,^{2,5-9} and Graves' disease accounts for 85% of cases.^{10,11} Left untreated, hyperthyroidism poses serious risks for both fetus and mother,⁹ including preeclampsia, thyroid storm, heart failure, miscarriage and stillbirth, prematurity, intrauterine growth restriction, and neonatal thyrotoxicosis.³

Favourable fetal and maternal outcomes require control of the mother's abnormal thyroid function.³ The amides propylthiouracil and methimazole are thyroid peroxidase analogues, capable of reducing the synthesis of T₃ and T₄ while also blocking iodine release. The goal of therapy with these agents is to maintain the mother's serum free T₄ concentration in the high to normal range using the lowest possible drug dose.¹² Both drugs readily cross the placenta with similar kinetics of placental transfer.¹³

PTU has been considered the drug of choice during pregnancy, mostly because MMI has been associated with characteristic teratogenic effects including aplasia cutis congenita, choanal atresia, tracheoesophageal fistulas, and other less common abnormalities.¹ ACC is a localized absence of skin in the occipital area of the scalp, usually ranging in size from 0.3 to 5 cm.¹⁴ Rarely, the lesion may extend below the scalp and

include absent skull bone and dura; in this case, surgical intervention is required. The incidence of ACC ranges from 0.03% to 0.05% (0.6 to 1 per 2000 births).¹⁴

CA is a rare obstruction of the posterior choanae with an incidence of approximately 0.01% to 0.05% (1 to 5 per 10 000 births).^{15,16} The obstruction can be unilateral or bilateral, bony or membranous.⁷ In cases of bilateral obstruction, surgical intervention is required.

In addition, MMI has been also associated with the following anomalies:

1. facial abnormalities including broad forehead, broad nasal bridge, arched eyebrows¹⁵
2. hypoplastic nipples⁷
3. gastrointestinal manifestations such as esophageal atresia and tracheoesophageal fistula¹⁷
4. growth restriction and delayed development.^{5,14,17,18}

While ACC is the more common malformation associated with MMI, it has mostly benign implications, while CA and other features of the embryopathy have greater clinical effects on the newborn.

Although several studies have supported an association between MMI therapy and ACC, CA, and tracheoesophageal fistulas,^{7,16} others have failed to show such associations.^{19,20}

Traditionally, PTU has been considered a superior choice for treatment in pregnant women because it has not been associated with teratogenicity. However, unlike MMI, few studies of PTU teratogenicity have been published.¹⁴

During the last two decades a growing number of reports have raised concerns about PTU-induced hepatotoxicity.²¹

This has led to the issuing of a black box warning by the Food and Drug Administration in the United States. Only sporadic cases reporting liver toxicity following treatment of PTU during pregnancy have been reported.²¹

The objective of the present study was to systematically review the relevant literature in order to assess the maternal and fetal risks of treatment with MMI and PTU during pregnancy and provide clarifications for evidence-based treatment of gestational hyperthyroidism.

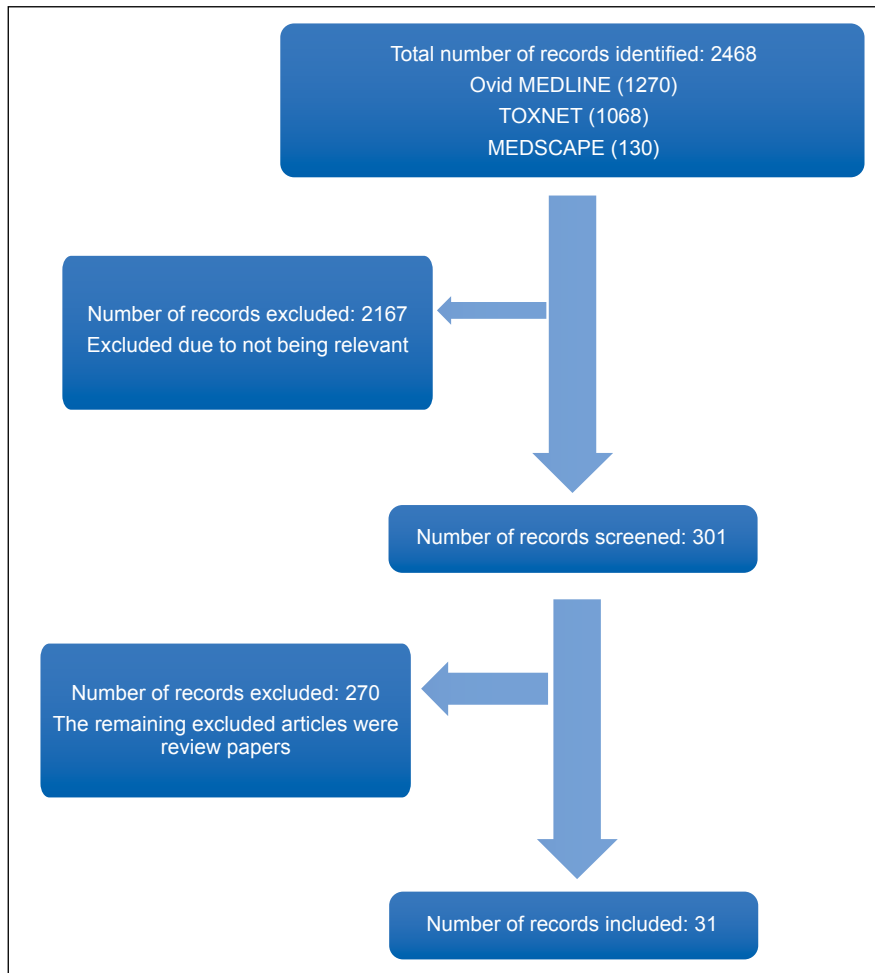
METHODS

The following electronic databases were searched: Ovid Medline (articles published from 1948 to March 2012), EMBASE (articles published from 1947 to March 2012),

ABBREVIATIONS

ACC	aplasia cutis congenita
CA	choanal atresia
FDA	United States Food and Drug Administration
MMI	methimazole
PTU	propylthiouracil
T ₃	tri-iodothyronine
T ₄	thyroxine

Flow chart of selected studies



and TOXNET, TOKLINK, Medscape, EBSCO, and Google, with no restrictions on language or year of publication. The last search was run on March 15, 2012. Our search strategy included the following MeSH terms: “methimazole” and/or “propylthiouracil” combined with “pregnancy,” “pregnancy adverse outcome” or “malformations” or “cutis aplasia” or “choanal atresia” or “embryopathy” or “hepatitis.” The search was limited further to human data and clinical trials. Reference lists of relevant review papers and all selected articles were hand-searched to identify additional trials.

Exclusion criteria were (1) studies including anti-thyroid therapies other than PTU and MMI; and (2) studies with insufficient data to allow interpretation of results.

RESULTS

A total of 2468 publications were identified. After applying the exclusion criteria, 31 publications were reviewed

to evaluate the adverse effects of MMI or PTU. These included cohort and case-control studies and case reports or case series (Figure). No RCTs were identified.

Methimazole

Cohort studies

Several retrospective cohort studies addressed MMI teratogenicity, and only a few of these studies evaluating MMI teratogenicity identified cases with one of the features associated with fetal MMI.^{19–20,22–24} Di Gianantonio et al. conducted a multicentre cohort study of MMI-associated malformations after intrauterine exposure to MMI and carbimazole.²² This study identified 241 infants who were exposed to MMI and carbimazole in utero and reported one case of CA and one of esophageal atresia in the exposed group. The authors concluded that these malformations might have a higher than expected incidence in fetuses exposed to MMI and carbimazole between three and seven weeks’ gestation.²²

In a study with a similar sample size, Momotani et al. identified 243 women exposed to MMI during the first trimester of pregnancy and found no such anomalies.¹⁹ In this comparative study, other unrelated adverse anomalies were reported, including one case of omphalocele and one ear lobe abnormality. Overall, there were significantly fewer malformations in the MMI-exposed group than in a comparison group of women with untreated hyperthyroidism. In a cohort study by Mujtaba and Burrow, two cases of ACC were identified among 15 newborns exposed prenatally to MMI.²³ In another cohort, two mild cases of ACC were reported among 15 newborns exposed prenatally to MMI.²⁴

In a cohort of 36 newborns exposed to MMI in utero, Wing and colleagues found a rate of major malformations of 2.7%. They did not identify any cases of scalp defects or CA.²⁰

Case-control studies

Two case-control studies investigated an association between MMI and specific malformations that had been associated with MMI.^{7,25} Barbero et al. compared the incidence of CA in MMI-exposed pregnancies and control subjects.⁷ Mothers of cases ($n = 61$) and control subjects ($n = 183$) were interviewed to record sociodemographic status, obstetrical and genetic history, and exposure to different agents during pregnancy; specifically, detailed information regarding hyperthyroidism and MMI intake was obtained. Prenatal exposure to maternal hyperthyroidism treated with MMI was identified in 16.4% of cases (10/61) and only 1.1% (2/183) in the control group (OR 17.75; 95% CI 3.49 to 121.40). Cases and control subjects did not differ in level of parental education, paternal occupation, twinning, maternal parity, and other exposures during pregnancy. Facial features in cases showed some similarities. These data suggest that prenatal exposure to maternal hyperthyroidism and treatment with MMI is associated with CA. In addition, based on their cases and a critical review of the literature, the authors proposed that the mother's disease, and not the treatment with MMI, might be the causal factor.⁷

Van Dijke et al. reviewed 49 091 birth records of neonates with ACC and reported 13 cases of scalp skin defects (0.03%). None of the mothers of these neonates were exposed to MMI during pregnancy. Among 24 records of pregnant women treated with MMI and carbimazole, no child was affected by ACC.²⁵

Case reports

MMI-related adverse fetal outcomes have been reported in numerous case reports and case series. Fifteen cases

with ACC, 12 with CA, and three with other features of MMI embryopathy have been described. One neonate had both CA and ACC together with other anomalies^{26,27}; another neonate had choanal and esophageal atresia with other severe cardiac and abdominal malformations, and died from post-surgical infection.²⁷ A neonate with ACC, esophageal atresia, and facial dysmorphism has also been reported.²⁸ Another was born with CA, facial dysmorphism, and developmental delay.²⁹ Of potential significance, one case report described a neonate who had been exposed to MMI only after the eighth week of gestation as having bilateral CA.³⁰ The time of exposure (at eight weeks) is relatively late in term of embryogenesis.

Cases with umbilical hernia ($n = 1$)^{20,26} and omphalocele ($n = 4$)^{19,26} have been reported after exposure to MMI. Of note, five sets of twins have been described, and in two of the sets both twins were identically affected: one set of twins had ACC and the other had CA. Unfortunately, zygosity was not reported in all of the twins.^{6,26,28,31,32}

Propylthiouracil

Several cohort studies of PTU exposure during pregnancy met our inclusion criteria. A prospective observational controlled cohort study of PTU-exposed pregnancies in women counselled by the Israeli Teratology Information Service between the years 1994 and 2004 involved 115 PTU-exposed pregnancies and 1141 control subjects exposed to non-teratogenic drugs.⁵ The rate of major anomalies was comparable between the groups (1.3% for PTU exposure [1/80] and 3.2% for control subjects [34/1066]; $P = 0.5$). Hypothyroidism was found in 9.5% of fetuses or neonates (56.8% of whom had goitre). Neonatal hyperthyroidism, possibly resulting from maternal disease, was found in 10.3%. Goitres diagnosed prenatally by ultrasound were successfully treated in utero by adjustment of the maternal dose of PTU. In most cases, neonatal thyroid function normalized during the first month of life without treatment. The median birth weight in neonates exposed to PTU (3145 g, interquartile range 2655 to 3537 g) was lower than in control subjects (3300 g, interquartile range 2968 to 3600 g) ($P = 0.018$).

Osorio and colleagues described the management of 19 hyperthyroid pregnant women between 1987 and 1991.³³ Of these, 18 had diffuse goitre and one had nodular goitre. In 10 of the women, thyrotoxicosis preceded pregnancy. PTU was used in 17 women (7 throughout pregnancy); five required surgery because of a poor response, one received propranolol, and one patient was not treated because of lack of attendance. Caesarean section was performed in 12 women, five had a vaginal delivery, one had a miscarriage at 20 weeks' gestation because of a neurological malformation,

and one patient was lost to follow-up before delivery. The newborn of the untreated woman had neonatal thyrotoxicosis, but the remaining 16 neonates did not show evidence of thyroid dysfunction. Newborns whose mothers received PTU until delivery had significantly lower reverse T_3 levels and non-significant changes in levels of T_4 and T_3 . At the end of the observation period, eight women were euthyroid, three were hypothyroid (2 after ^{131}I treatment and 1 after surgery), four remained on PTU, and four were lost to follow-up.

Wing and colleagues described 99 cases of gestational exposure to PTU, with a normal rate of major birth defects (3%).²⁰

A single case report published in 2011 described ACC in a surviving twin after in utero PTU exposure. The authors could not attribute this malformation to a possible vascular etiology (suggested by a vanishing twin) or to maternal hyperthyroidism. They concluded that coincidence of PTU exposure and ACC seems unlikely.³⁴

Neurodevelopmental Effects

Eisenstein and colleagues examined the intellectual capacity of 31 subjects aged four to 23 years, born to women with Graves' disease who received anti-thyroid drugs throughout pregnancy.²⁴ Fifteen of the subjects were exposed to MMI (40 to 140 mg/week) and 16 were exposed to PTU (250 to 1400 mg/week). IQ was assessed using the Wechsler test appropriate for age. Twenty-five unexposed siblings served as control subjects. The exposed and unexposed groups did not differ in total IQ. The groups scored equally in verbal and performance skills and in each of six main sub-categories of the tests. There was no difference in performance between subjects exposed to MMI and those exposed to PTU, or between those exposed to higher doses (> 40 mg of MMI/week or > 600 mg PTU/week) and lower doses. All children were euthyroid at birth and none had goitre. The authors concluded that exposure to MMI or PTU during pregnancy in doses sufficient to control maternal hyperthyroidism does not pose any threat to intellectual capacity in the offspring.

Hepatotoxicity

Over the past 20 years, 22 serious cases of liver injury (resulting in 9 deaths and 5 liver transplants) have been reported to the FDA and to the Adverse Event Reporting System.³⁵ The estimated occurrence of PTU-related acute liver failure is 1 in 10 000 exposed adults.²¹ This is believed to be an immune allergic response that occurs only with PTU. In severe cases, fatality rates of up to 25% to 50% have been reported.²¹ The United Network for Organ Sharing reported 16 liver transplants performed for PTU-related liver failure in adults.³⁵ In children, PTU-related

liver impairment appears to be more frequent, with the prevalence estimated at 1 in 2000 children.¹⁵ Despite the publicity and recommendations that PTU should not be used in children, at least two children suffered from serious liver impairment after exposure to PTU: one had liver failure that required liver transplantation, and the other had acute liver injury, pending liver failure, that eventually resolved spontaneously. On April 21, 2010, the FDA "black box warning" about use of PTU was issued.¹⁵ The FDA made the following recommendations:

1. PTU should not be prescribed as the first-line treatment agent in children or adults.
2. However, because of the multiple reports of MMI teratogenicity, PTU should be prescribed for hyperthyroidism during the first trimester of pregnancy, at least until more is known regarding the teratogenicity of MMI.
3. PTU is recommended in preference to MMI in life-threatening thyrotoxicosis or thyroid storm because of its superiority in inhibiting peripheral conversion of T_4 to T_3 .
4. PTU can be used in individuals who have experienced adverse responses to MMI (other than agranulocytosis) and for whom radioiodine or surgery are not treatment options.³⁵

Although hepatotoxicity in adults and children is well documented, there are limited data regarding hepatotoxicity in pregnant women and even fewer regarding effects on the fetus, leading to conflicting opinions. We identified two case reports of hepatotoxicity in pregnant women with Graves' disease, one of them requiring a liver transplant and the other having resolution after discontinuation of PTU.^{36,37} In June 2012, we encountered a third case in Toronto (unpublished case). In neonates, the most significant case described neonatal hepatitis that was positive for newborn lymphocyte transformation test for PTU.³⁸ This test suggests an immunological reaction to PTU through lymphocytes. This case describes prenatal exposure to PTU given for maternal Graves' disease.³⁸ On the basis of the positive lymphocyte test, the authors concluded that this was a clear case of neonatal PTU-induced hepatotoxicity.

Less obvious cases were reported by Hare and Kitzmiller in five pregnant women with both Graves' disease and juvenile diabetes who were treated with PTU.³⁹ Four of the infants had hyperbilirubinemia, which might have been attributed to prenatal PTU exposure but might also have indicated liver impairment due to the underlying diabetes. In contrast, Devi et al. reported a case of hyperthyroidism

Details of papers included in the systematic review

Study and sample size	Drugs, daily dose, and timing of exposure during pregnancy	Major related malformations (ACC, CA, EA embryopathy, liver abnormalities)	Pregnancy and neonatal outcome
Momotani et al. ¹⁹ (N = 243)	MMI 10 to 1680 mg 1st trimester	None	1. Malformation of ear lobe > 10 weeks 2. Omphalocele
Wing et al. ²⁰ (N = 135) PTU = 99 MMI = 36	N/A	None	1. Severe pulmonic stenosis 2. Ventricular septal defect 3. Patent ductus arteriosus
Barbero et al. ⁷ (N = 61) Case-control for CA (N = 12)	MMI 20.5 mg	None	Congenital inguinal hernia NS
Rosenfeld et al. ⁵ (N = 115)	MMI 20.5 mg	CA-10 10/61 vs.2/183, OR 17.75, 95% CI (3.49 to 12.4)	N/A
Rosenfeld et al. ⁵ (N = 115)	PTU 150 mg (100 to 200 mg) 98 treated throughout pregnancy 15 treated from start of 2nd trimester 2 treated from start of 3rd trimester	None	1. Hip dysplasia NS 2. Low birth weight (3145 vs. 3300 g) 3. Hypothyroidism 9.5%
Osorio et al. ³³ (N = 19)	PTU used in 17 women, 7 throughout the entire pregnancy	None	PTU treated had lower rT ₃ levels.
Eisenstein et al. ²⁴ (N = 31) MMI = 15 PTU = 16	MMI 40 to 140 mg/week PTU 250 to 1400 mg/week	ACC minor × 2	1. Anal atresia
Mujtaba and Burrow ²³ (N = 26)	PTU 100 to 400 mg MMI 15 mg throughout pregnancy MMI 15 mg 1st trimester, and then 5 mg throughout pregnancy	None Case 1. ACC Case 2. ACC	Thyrotoxicosis (2), mild thyrotoxicosis and small goitre (1), aortic atresia: infant death Imperforated anus None
Ferraris et al. ²⁶ (N = 3)	MMI 10 mg until 8 weeks, then PTU 200 mg until delivery MMI 40 to 20 mg throughout pregnancy	Case 1. CA and ACC Case 2. dizygotic twins: ACC/None	Umbilical hernia, pilonidal sinus, limb hypertonia Small omphalocele None
Iwayama et al. ³² (N = 2)	MMI 15 to 30 mg/kg/day	Monozygotic twins: ACC/none	
Karg et al. ⁴⁶ (N = 1)	MMI 150 g/day then PTU from 6 weeks until delivery	ACC	Facial dysmorphism
Barbero et al. ⁷ (N = 3)	MMI 15 mg throughout pregnancy MMI 20 mg throughout pregnancy	Case 1. twins CA/CA CA	A. Facial dysmorphism B. Facial dysmorphism (same) Facial dysmorphism (similar) Micrognathia
Nakamura et al. ⁴⁷ (N = 1)	MMI 10 mg 1st trimester	ACC bilateral	N/A
Valdez et al. ⁴⁸ (N = 1)	MMI 50 g 1st trimester, and then 30 mg until delivery	Embryopathy	
Clementi et al. ¹⁷ (N = 1)	MMI 20 mg until 6 weeks, then PTU till delivery	CA	Facial dysmorphism Ear malformation Hypertonia
Ozgen et al. ⁴⁹ (N = 1)	MMI in the first 3 months of pregnancy	CA Embryopathy	
Hall ⁵⁰ (N = 1)	MMI in the first 2 months of pregnancy PTU for last 7 months of pregnancy	CA	Facial dysmorphism
Milham and Ellege ³¹ (N = 3)	N/A	Case 1. twins ACC/ACC Case 2. ACC	N/A

Continued

Continued

Study and sample size	Drugs, daily dose, and timing of exposure during pregnancy	Major related malformations (ACC, CA, EA embryopathy, liver abnormalities)	Pregnancy and neonatal outcome
Greenberg ²⁹ (N = 1)	MMI	CA Embryopathy	None
Van Dijke et al. ²⁵ (N = 1)	MMI 20 mg throughout pregnancy Thyroid hormone extract 50 mg	CA	
Johnsson et al. ²⁷ (N = 1)	MMI 30 mg until 18 weeks partial thyroidectomy Metoprolol 150 mg stopped at 5 weeks	CA, EA	Preterm labour at 27 weeks, tracheoesophageal fistula omphalocele, multiple ventricular septal defects Infant death from post-surgical infection
Mandel and Cooper ¹⁴ (N = 1)	MMI 30 to 90 mg until 20 weeks partial thyroidectomy	ACC	
Vogt et al. ⁵¹ (N = 1)	MMI 40 mg until 12 weeks, then reduced to 20 mg	ACC	
Farine et al. ⁵² (N = 1)	MMI 10 mg until confirmation of pregnancy and then switched to PTU	ACC	
Gripp et al. ²⁸ (N = 3)	15 mg MMI until 6 weeks, then nothing for 4 weeks, switched to PTU 50 mg at 10 weeks plus propranolol dose Thyroidectomy 16 weeks Fluoxetine MMI 40 mg decreased to 10 mg at 36 weeks due to hypothyroidism Propranolol 60 mg	EA Multiple area ACC Twins A. CA	Facial dysmorphism Clinodactyly Sensorineural hearing loss Facial dysmorphism, ear abnormality, clinodactyly, single palmar crease, 46XX B. Facial dysmorphism
Kim et al. ²¹ (N = 1)	MMI during first 9 weeks	ACC	
del Cacho and Frias ³⁰ (N = 1)	Methimazole 10 mg/day from 8th week	Bil CA	Facial dysmorphism
Ono et al. ⁵³ (N = 1)	MMI used during pregnancy	None	Omphalocele
Morris et al. ³⁴ (N = 1)	PTU till 25 weeks gestation	Maternal fulminant hepatic failure encephalopathy, coagulopathy. Coma-thyrotoxicosis Liver transplant	Post transplant Caesarean section at 26 weeks IUGR Stillbirth
Parker ³⁷ (N = 1)	PTU 450 mg until 20 weeks Hepatitis Switched to propranolol and then MMI 15 mg with resolution	Thyrotoxic Non-viral hepatitis Resolution after discontinuation of the PTU. Positive lymphocyte transformation test for PTU (negative for MMI)	N/A-assuming uneventful.
Hayashida et al. ³⁸ (N = 1)	PTU 250 mg/day Methyldopa 250 mg/daily Propranolol 80 mg/daily until 30 weeks	Thyrotoxic	Neonatal hyperthyroidism, Non-viral hepatitis. Positive lymphocyte transformation test for PTU
Lollgen et al. ⁵⁴ (N = 1)	PTU used during pregnancy	ACC in surviving twin	Co-twin demise

EA: esophageal atresia

in pregnancy in which the mother was treated with PTU and developed maternal hepatitis.⁴⁰ The fetal liver was not affected. From this single case, Devi et al. concluded that PTU-induced fetal hepatitis is an extremely rare side effect that should not affect the mode of therapy. As both PTU and MMI cross the placenta and are detected in the fetal circulation,¹³ it seems that PTU treatment should be discontinued after the first trimester of pregnancy, given the high probability of PTU toxicity in children and one reported case of newborn liver impairment.³⁸

Data Synthesis

The present systematic literature review included published studies evaluating the outcome of prenatal exposure to MMI and PTU. MMI exposure was mostly associated with ACC¹⁵ and CA.²³ Because of the rare occurrence of these malformations, most cohort studies (each containing several hundred cases) could not detect them.^{19–20,22–24} In contrast, a case–control study clearly delineated the contribution of MMI to cases of CA.^{7,25} A similar case–control study has failed to prove an association between MMI and ACC⁷; ACC is an anomaly that occurs at a rate of 1:20 000, an extremely low absolute risk, despite having a high odds ratio of 17.⁷ These principles are important in counselling women taking MMI.

Rosenfeld et al. predicted that 20 cases of ACC should occur in 100 million births, based on an incidence of ACC of 0.05% and an incidence of hyperthyroidism in pregnancy of 0.2%.⁵ Approximately one third of these are treated with MMI.⁴¹

It is important to consider that uncontrolled maternal hyperthyroidism per se may theoretically cause congenital malformations and adverse pregnancy outcome. Momotani et al. reported that treatment of maternal hyperthyroidism with either PTU or MMI was associated with a reduced rate of congenital malformations.¹⁹ Their study included 643 neonates born to mothers with Graves' disease and reported a 6% rate of congenital malformations in mothers with uncontrolled hyperthyroidism, much higher than in the PTU and MMI-treated groups. In a case–control study, Barbero et al. were unable to attribute the higher rate of CA to either MMI exposure or to maternal hyperthyroidism.⁷ In fact, these authors raised the suspicion that this malformation may be attributed to the underlying hyperthyroidism and not to MMI exposure; their suspicion was based on the fact that exposure to MMI was relatively late in pregnancy (at 28 weeks in one of their 10 cases), and not during the critical embryogenic period earlier in pregnancy (4 to 10 weeks). However, in most cases with MMI-associated embryopathy in the case reports we reviewed, the exposure to MMI did indeed

occur in the first trimester during the critical embryogenic period, and occurred mostly in mothers with uncontrolled thyrotoxicosis. The fact that CA has been documented with PTU exposure only once provides strong evidence that it is not the hyperthyroid status itself but MMI exposure that is the cause of embryopathy.

Although it is still debatable whether the rates of some of MMI-related malformations are above the baseline risk in the general population, or may be related to hyperthyroidism per se, these adverse outcomes have not been reported in association with PTU treatment. From a clinical practice perspective, the MMI-related malformations can have serious health implications. The possible teratogenic effect of MMI therefore cannot be ignored, and use of the drug should be avoided in the first trimester of pregnancy.

There is significantly less available evidence for potential teratogenicity with use of PTU. In cohort studies we found no evidence of an increased risk of fetal malformations. Although a few cases of transient neonatal hypothyroidism and low birth weight have been reported,⁵ these are not considered to be of significant clinical relevance. Based upon the available cohort studies, and the lack of homogenous case reports, it is conceivable that PTU is not a human teratogen. However, a major concern regarding PTU treatment arises from its emerging potential for serious hepatotoxicity.

Both MMI and PTU have been shown to cause agranulocytosis,^{42,43} and both drugs can cause fever and arthralgia.⁴⁴ Importantly, both drugs, when administered at high doses, can cause fetal and neonatal hypothyroidism; therefore, vigilant monitoring of maternal thyroid function and of sonographic signs of fetal hypothyroidism is warranted.⁴⁵

CONCLUSION

Our systematic review has provided reasonable evidence that MMI has rare but clinically significant teratogenic effects when the fetus is exposed to the drug in the first trimester, and that PTU has potential for severe hepatotoxic sequelae. Thus, it is reasonable to recommend that in pregnant women with hyperthyroidism, PTU should be administered during the first trimester and switched thereafter to MMI for the remainder of the pregnancy.

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