

# Teratogen Update: Antithyroid Drugs—Methimazole, Carbimazole, and Propylthiouracil

ORNA DIAV-CITRIN<sup>1</sup> AND ASHER ORNOY<sup>1,2\*</sup>

<sup>1</sup>The Israeli Teratogen Information Service, Israeli Ministry of Health, Jerusalem, Israel

<sup>2</sup>Laboratory of Teratology, the Hebrew University Hadassah Medical School, Jerusalem, Israel

## INTRODUCTION

Thyrotoxicosis occurs in about 0.2% of pregnancies and is caused most frequently by Graves disease (Burrow, '85; Kriplani et al., '94). Graves disease is an autoimmune disorder characterized by the production of antibodies, immunoglobulins of the IgG class, directed against thyroid stimulating hormone (TSH) receptors (Shoenfeld and Schwartz, '84). This results in the excess production of thyroid hormones. Because IgG antibodies pass through the human placenta, their transfer can induce stimulation of the fetal thyroid gland causing fetal hyperthyroidism (Hollingsworth, '83). Thyrotoxic fetuses have a high risk for prematurity, intrauterine growth retardation, craniostenosis, cardiac failure, fetal hydrops, and intrauterine death (Treadwell et al., '96; Zimmerman, '99). This is apparently unrelated to the status of maternal thyroid function and effectiveness of treatment (Hollingsworth, '83; Porreco and Bloch, '90).

Antithyroid drugs, which interfere with the synthesis of thyroid hormones, are the treatment of choice for thyrotoxicosis in pregnancy. Propylthiouracil (PTU), methimazole (MMI) and carbimazole (CMZ) are thioureylenes, which belong to the family of thioamides. The antithyroid compounds currently used in the United States are PTU and MMI. In the United Kingdom and Europe, CMZ, a carboxy derivative of MMI, is available, and its antithyroid action is due to its conversion to MMI after absorption. Although both PTU and MMI cross the placenta, MMI was originally reported to have a three times greater placental transfer than PTU (Marchant et al., '77). PTU is therefore preferred over MMI because of its lower transplacental passage (Farwell and Braverman, '96). It was recently suggested, however, that both drugs have similar kinetics of placental transfer (Mortimer et al., '97).

All antithyroid drugs may inhibit fetal thyroid function causing fetal hypothyroidism. This is usually transient with a return to the euthyroid state within several days or weeks after birth. (Kriplani et al., '94; Wing et al., '94; Vanderpump et al., '96;). For that reason, and because of the transplacental passage of maternal antithyroid antibodies, it may be important to assess fetal thyroid function in treated mothers with Graves disease either by Doppler echography or, in

selected cases, by fetal blood sampling (Porreco and Bloch, '90; Lutton et al., '97). Fetal hyperthyroidism can be treated by administration of PTU to the mother (Wallace et al., '95; Treadwell et al., '96). Infants of mothers with Graves disease who had been treated with antithyroid drugs may have hypothyroidism (due to drug transfer) or hyperthyroidism (due to the transfer of antibodies). It is therefore important to assess the thyroid function of each neonate born to a treated hyperthyroid mother, especially if thyroid enlargement is observed by ultrasonography (Brunner and Dellinger, '97; Momotani et al., '97; Zimmerman, '99).

This update will review the use of antithyroid drugs during pregnancy addressing the risk of congenital anomalies. Special attention will be given to the possible associations between in utero exposure to MMI and aplasia cutis congenita and a spectrum of congenital anomalies including choanal atresia. The risk of fetal goiter after treatment with all antithyroid drugs, and possible neurodevelopmental toxicity will also be discussed.

## PROPYLTHIOURACIL

### Animal data

Animal studies were carried out in mice, rats, and rabbits. Thyroid enlargement was observed in the offspring of rabbits (Krementz et al., '57; Mandel et al., '94) and guinea pigs (Peterson, '53) treated during pregnancy with propylthiouracil (PTU). Similar studies in rats and mice resulted in hypothyroidism in the offspring (Goldey et al., '95; Calikoglu et al., '96). The rate of major congenital anomalies was not increased in these animals.

### Effects of PTU on the developing human fetus

The frequency of congenital anomalies among children born to PTU treated hyperthyroid mothers does not seem to be increased. Momotani and Ito ('91) have

\*Correspondence to: Prof. Asher Ornoy, The Israeli Teratogen Information Service, Laboratory of Teratology, The Hebrew University, Hadassah Medical School, PO Box 12272, Jerusalem, Israel 91120. E-mail: ornoy@cc.huji.ac.il

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shown no increase in the rate of congenital anomalies in 65 children born to mothers treated with either PTU or MMI, in comparison to untreated mothers with Graves disease. Several series of reports on children born to hyperthyroid mothers treated with PTU failed to show any increase in the rate of major congenital anomalies (Holt et al., '70; Goluboff et al., '74; Wing et al., '94; Ghaneim and Atkins, '98).

#### **Fetal goiter associated with exposure to PTU**

Suppression of fetal thyroid function, which may occur only after the 10th week of pregnancy, when the fetal thyroid gland is actively functioning, occurs more often with PTU treatment than with MMI therapy (Burrow, '78; Becks and Burrow, '91). This may result in fetal thyroid hyperplasia and goiter while attempting to compensate for the hypothyroidism (Burrow, '78; Becks and Burrow, '91). Suppression of fetal thyroid occurs in 1–5% of neonates born to PTU treated mothers. Many of these infants exhibit neonatal goiter that can be diagnosed ultrasonographically in utero (Becks and Burrow, '91; Friedland and Rothchild, '00). Large goiters that can cause respiratory compromise in the newborn infant are rare (Becks and Burrow, '91). A combination of PTU and iodides or PTU and thyroid hormone are contraindicated in pregnancy because they are more goitrogenic than PTU alone (Mujtaba and Burrow, '75; Burrow, '78, '85, '93; Vanderpump et al., '96).

#### **Neurodevelopmental effects of in utero exposure to PTU**

Several studies have assessed the cognitive development of offspring of PTU or MMI treated hyperthyroid mothers. They found no difference in several developmental outcomes including intelligence between these children and controls (Burrow et al., '78; Messer et al., '90; Eisenstein et al., '92). These studies, however, do not seem to correlate the developmental outcome with the fetal thyroid function, and we have to presume that the children were euthyroid while in utero. This latter issue is important, because very little is known regarding the long-term effects of transient or permanent dysfunction of the fetal thyroid gland on postnatal brain development. Also in these studies attention span and learning ability were not fully ascertained and they may still be impaired despite a normal cognitive function, as observed in children born to heroin dependent mothers adopted at a young age (Ornoy et al., '01)

### **METHIMAZOLE AND CARBIMAZOLE**

#### **Animal data**

Methimazole (MMI) had no teratogenic activity in rabbits (Zolcinski et al., '64). MMI can cause abnormal development of rat embryos in vitro, although the concentration at which MMI disturbs rat embryogenesis is higher than that which is reached in hyperthyroid patients treated with clinical doses of MMI or carbima-

zole (CMZ) (Stanisstreet et al., '90). Postnatal behavioral alterations have been described in both mice (Rice et al., '87) and rats (Comer and Norton, '82; Albee et al., '89) after low-dose prenatal administration of MMI. Virtually all of the antithyroid agents have shown the capacity to induce fetal goiter in animals, as would be expected (Schardein, '93).

#### **APLASIA CUTIS CONGENITA**

Aplasia cutis congenita (ACC) is the congenital absence of skin and encompasses a spectrum of subtypes where either localized or widespread areas of skin are affected. The condition is rare with scalp ACC affecting 0.03% of the newborns (Van Dijke et al., '87). Although any part of the skin may be involved, most commonly the lesion is a 0.5–3 cm in size and involves the scalp. The lesion is solitary in 75% of cases, most commonly located at the parietal hair whorl. Only 8% of those lesions have associated congenital defects. Although the majority of these scalp defects occur sporadically, many familial cases have been reported. Heredity has been predominantly autosomal dominant, but recessive inheritance has also been implicated. Multiple etiologies have already been suggested for ACC. Genetic causes include chromosomal aberrations, namely trisomy 13 and deletion (4p) syndromes and single gene mutations such as focal dermal hypoplasia (Goltz syndrome). Other syndromes including ACC are Adams-Oliver syndrome, Setleis syndrome, Anderson-Hollister-Szalay syndrome, Johanson-Blizzard syndrome and a familial syndrome of 46,XY gonadal dysgenesis with multiple anomalies. It is also inherited with as an autosomal dominant trait in association with distal limb reduction anomalies and with postaxial polydactyly.

A small number of teratogens have also been linked with ACC. These include intrauterine infection (i.e., varicella zoster virus, herpes simplex virus), fetal exposure to drugs of abuse (i.e., cocaine, heroin, marijuana, and alcohol), or the antithyroid drugs, MMI and CMZ (Blunt et al., '92). The significance of MMI or CMZ treatment during pregnancy as a causal factor of scalp defects, however, remains a matter of debate.

#### **ACC and gestational exposure to MMI and CMZ**

Milham and Elledge ('72) were the first to suggest an association between congenital scalp defects and maternal ingestion of antithyroid drugs during pregnancy. They reported 11 cases of newborn scalp defects ascertained in Washington State by birth certificate report and physician questionnaire in a 6-month period. The lesions were single circular, punched out, ulcer-like midline defects of the scalp at the vertex or in the occipital area. Query of the mothers revealed that two of the 11 had taken MMI during pregnancy for hyperthyroidism. A third mother had taken thyroid hormone during her pregnancy for treatment of hypothyroidism. One of the mothers taking MMI delivered a set of fraternal twins both of whom had scalp defects. In

addition to the scalp defect, one of the twins also had a patent urachus requiring surgical repair (Milham, '85). Mujtaba and Burrow ('75) reported 21 women who had used MMI or PTU during pregnancy for hyperthyroidism. One who received MMI during two successive pregnancies gave birth to two siblings with scalp defects, one of whom also had imperforate anus. Bachrach and Burrow ('84) mention five verbally reported cases of ACC in infants whose mothers had been treated with MMI in pregnancy. Milham ('85) reported four additional cases of MMI associated scalp defects. One of the four cases had an associated umbilical defect, patent vitelline duct. In this case the mother had been treated with CMZ. Van Dijke et al. ('87) report a case of a newborn with congenital scalp defects whose mother had taken MMI and thyroid hormone extract during pregnancy. Another case of ACC associated with maternal exposure to MMI has been reported with scalp hypoplasia and elevated alpha-fetoprotein (Kalb and Grossman, '86; Farine et al., '88). Tanaka et al. ('89) report a case of multiple congenital scalp defects in an infant whose mother had been treated with MMI during pregnancy. Dutertre et al. ('91) report a case of ACC in an infant whose mother had been treated with CMZ during pregnancy. Martinez-Frias et al. ('92) identified one child with ACC prenatally exposed to CMZ because of maternal hyperthyroidism. Sargent et al. ('94) describes a neonate with multiple areas of ACC and the stigmata of scalp-ear-nipple syndrome after in utero MMI exposure. Mandel et al. ('94) reported a case of ACC on the vertex of the head after in utero exposure to MMI. Vogt et al. ('95) reported a child with ACC whose mother was treated with MMI during pregnancy. Martin-Denavit et al. ('00) recently reported a girl with ACC of the scalp, with a combination of signs including abnormalities of various tissues of ectodermal origin (minor facial abnormalities, areas of hyperpigmented skin, two supernumerary nipples, bilateral syndactylies, dystrophic fingernails, and epilepsy). Her mother suffered from Graves disease and had been treated with MMI during pregnancy.

Martinez-Frias et al. ('92) observed a significant increase in the prevalence of ACC during the 1980s from 0.33/10,000 to 1.11/10,000 infants ( $P < 0.005$ ) in some areas of Spain. It was suggested that this increase was associated with illicit addition of MMI, with or without clenbuterol, a  $\beta$ -agonist, to animal feed as a weight enhancer. The new cases of ACC in the Spanish Collaborative Study of Congenital Malformation (SCSCM) were predominantly from regions where poisoning from clenbuterol was reported.

Contrary to the suggestive evidence listed above, several investigators reported in a retrospective approach lack of association between ACC and MMI or CMZ treatment during pregnancy. Momotani et al. ('84) have reported 243 infants whose mothers had been treated with MMI during pregnancy (117 mothers were hyperthyroid and 126 euthyroid). They were compared to infants of 400 mothers (350 euthyroid and 50 hyperthyroid) who did not receive MMI. None of the

children had ACC. Van Dijke et al. ('87) reviewed 49,091 birth records and found that 25 children (0.05%) had congenital skin defects, which were confined to the scalp in 13 (0.03%). Examination of patient files showed that none of the mothers of these children had used antithyroid drugs. They also found records of 24 mothers who had received treatment in the first trimester of pregnancy with MMI or CMZ and none of these children had skin defects. In a series of 27 (Kriplani et al., '94) and 36 (Wing et al., '94) children whose mothers were treated with MMI or CMZ during pregnancy, no cases of ACC were observed. In a recent multi-center ENTIS (European Network of Teratology Information Services) study reported by Di Gianantonio et al. (in press) of 241 pregnant women treated with MMI during pregnancy, none of the infants had ACC.

In summary, over a two-decade period, more than 18 cases of scalp ACC have been reported in possible association with MMI or CMZ treatment during pregnancy (Table 1), with further support from the SCSCM. There was, however, no support to such an association from prospective cohort studies. Even relatively large cohort studies are not big enough to detect an association with a rare defect as ACC. The lack of reported cases of scalp ACC after PTU administration in pregnancy is interesting. PTU is prescribed more frequently than MMI in hyperthyroidism and especially in pregnancy. Assuming a spontaneous incidence of 0.03% for scalp ACC, and a 0.2% incidence of hyperthyroidism in pregnancy, (approximately a third of whom are treated with MMI), 20 cases of ACC are predicted in 100 million births. We have no estimate of the unreported cases. A causal relationship between the use of MMI or CMZ during pregnancy and scalp ACC cannot be excluded. Based on the available data, a true risk estimate cannot be derived. The possible association between in utero exposure to MMI or CMZ and scalp ACC is probably weak. Table 1 summarizes the published studies.

#### **Congenital anomalies associated with in utero exposure to MMI**

Momotani et al. ('84) examined 643 neonates from mothers with Graves disease for major malformations of external organs. The prevalence of major congenital anomalies did not differ between 243 neonates exposed to MMI in utero (0.8%) and 400 unexposed neonates (1.0%).

#### **Is there a specific 'MMI syndrome'?**

An unusual pattern of congenital anomalies has been reported in several children whose mothers were treated with MMI or CMZ during pregnancy (Greenberg, '87; Ramirez et al., '92; Hall, '97; Wilson et al., '98; Clementi et al., '99). It has been suggested that this may represent a rare MMI embryopathy. Manifestations include choanal atresia, often with other gastrointestinal anomalies such as esophageal atresia with tracheo-esophageal (T-E) fistula, minor facial and skin dysmorphic features, growth restriction and develop-

TABLE 1. ACC in association with in utero exposure to MMI or CMZ

| Reference                                  | Neonates with scalp defects          | Solitary vs. multiple ACC | MMI/CMZ exposure | Additional defects  | Comments   |
|--|--------------------------------------|---------------------------|------------------|---|--|
| Milham and Elledge, '72                    | 3 (1 set of twins) of 12             | Solitary in all           | MMI              | One of the twins had patent urachus requiring surgical repair | Another mother with an offspring with scalp defect was on thyroid hormone for hypothyroidism |
| Mujtaba and Burrow, '75                    | 2 siblings                           | Multiple in at least 1    | MMI              | 1 with imperforate anus                                       |  |
| Bachrach and Burrow, '84                   | Mention of 5 verbally reported cases |                           | MMI              |   |  |
| Milham, '85                                | 4                                    | Solitary in all           | 3 MMI<br>1 CMZ   | None in 3<br>Patent vitelline duct in 1                       |  |
| Kalb and Grossman, '86; Farine et al., '88 | 1                                    | Solitary                  | MMI              | Skull hypoplasia  | Elevated alpha-fetoprotein   |
| Van Dijke et al., '87                      | 1                                    | Multiple                  | MMI              | None  | The mother was also on thyroid hormone extract   |
| Tanaka et al., '89                         | 1                                    | Multiple                  | MMI              | None  |  |
| Dutertre et al., '91                       | 1                                    | Solitary                  | CMZ              | None  |  |
| Martinez-Frias et al., '92                 | 1                                    |                           | CMZ              | None  |  |
| Mandel et al., '94                         | 1                                    | Solitary                  | MMI              | None  |  |
| Sargent et al., '94                        | 1                                    | Multiple                  | MMI              | Scalp-ear-nipple syndrome                                     |  |
| Vogt et al., '95                           | 1                                    | Solitary                  | MMI              | None  |  |
| Martin-Denavit et al., '00                 | 1                                    | Multiple                  | MMI              | Ectodermal abnormalities                                      |  |
| Total                                      | 18                                   |                           |                  | 5/18  |  |

mental delay. Other possible cases include those reported by Shikii et al. ('89) and Johnsson et al. ('97), insufficiently described for full assessment. In all these cases exposure occurred before the 7th week of gestation. Many of the published cases have the clinical characteristics of CHARGE association (Koletzko and Majewski, '84). Various isolated major congenital anomalies without choanal atresia have been described among infants whose mothers had taken MMI during pregnancy (cerebral atrophy, DiGeorge syndrome, transposition of great vessels (Sugrue and Drury, '80; Kawamura et al., '89; Shikii et al., '89).

Di Gianantonio et al. (in press) prospectively studied pregnancy outcome in 241 MMI exposed women and compared it to that observed in a control group exposed to non-teratogenic agents. There was no increase in the overall rate of major anomalies between the two groups. Two exposed newborns were affected with one of the major malformations that are a part of the postulated MMI embryopathy (choanal atresia and esophageal atresia). The data are summarized in Table 2. Although further studies are needed to substantiate a causal relationship between MMI treatment during the first trimester of pregnancy and the above-described embryopathy, we should remember that no such cases were described after PTU treatment. This is, therefore, of concern, and may warrant preference of PTU over MMI treatment during pregnancy.

#### Fetal goiter associated with in utero exposure to MMI or CMZ

Congenital goiter, hypothyroidism or both, occasionally occur among infants whose mothers had been treated with MMI or CMZ during pregnancy (Refetoff et al., '74; Sugrue and Drury, '80; Ramsay et al., '83; Burrow, '85, '93; Becks and Burrow, '91; Mestman et al., '95; Momotani et al., '97). This effect is biologically plausible based on the pharmacological effect of placentally transferred drug after the 10th gestational week when the fetal thyroid begins to function. As mentioned earlier, it is also supported by animal data. In most cases these problems are transient and spontaneously resolve in a few months.

#### Neurodevelopmental effect of gestational exposure to MMI or CMZ

Psychometric assessment of 16 children born to mothers had been treated with MMI or CMZ during pregnancy showed no difference in scores from controls (Messer et al., '90). Similarly, no difference in intellectual capacity was observed between 15 subjects born to women with Graves disease who received MMI (40–140 mg/week) throughout pregnancy and their siblings who were not exposed to MMI in pregnancy (Eisenstein et al., '92). Normal intellectual function and somatic growth was de-

TABLE 2. Pattern of anomalies in children exposed to MMI in utero

| Reference                                 | Antithyroid drug                    | GA, weeks | BW, g  | Major congenital anomalies         | Facial dysmorphism | Neurodevelopment | Additional problems             | Neonatal thyroid function |
|---|-------------------------------------|-----------|--------|------------------------------------|--------------------|------------------|---------------------------------|---------------------------|
| Mujtaba and Burrow, '75<br>Case 3         | MMI                                 |           | 2520   | Imperforate anus, hypospadias, ACC |                    |                  |                                 |                           |
| Greenberg, '87                            | MMI                                 |           | 2190   | CA, athelia                        | Present            | Delayed          | Mild sensorineural hearing loss | Euthyroid                 |
| Shikii et al., '89                        | MMI                                 | 29        | 1290   | Brain atrophy                      | Moderate           | Delayed          | Hydrops fetalis, West Syndrome  | Hypothyroid               |
| Ramirez et al., '92<br>Case 1             | MMI                                 | 36        | 1560   | EA + TEF                           | Mild               |                  | Hypotonia, died on day 6        | Hypothyroid               |
| Ramirez et al., '92<br>Case 2             | MMI                                 | 38        | 2455   | EA + TEF                           | Absent             |                  | Died on day 5                   | Hypothyroid               |
| Johnsson et al., '97                      | MMI (until week 18)                 | 27        | 750    | CA, EA, TEF, VSD                   |                    |                  | Died at 6 weeks                 |                           |
| Hall, '97                                 | MMI T1<br>PTU T2-3                  |           | Normal | CA, coloboma, renal pelvis ectasia | Severe             |                  |                                 |                           |
| Wilson et al., '98                        | CMZ                                 | 34        | 2070   | CA                                 | Severe             | Delayed          | Hypotonia                       | No goiter                 |
| Clementi et al., '99                      | MMI until week 6<br>PTU from week 7 | 31        | 1470   | CA, EA + TEF                       | Severe             | Delayed          |                                 | Euthyroid                 |
| Di Gianantonio et al., in press<br>Case 4 | MMI                                 |           |        | CA                                 |                    |                  |                                 |                           |
| Di Gianantonio et al., in press<br>Case 9 | MMI                                 |           |        | EA                                 |                    |                  |                                 |                           |

\*T, trimester; GA, gestational age at delivery; BW, birth weight; CA, choanal atresia; EA, esophageal atresia; TEF, tracheo-esophageal fistula; VSD, ventricular septal defect.

scribed in 25, 3–13 years old children exposed in utero to CMZ (McCarroll et al., '76). Contrary to the negative studies listed above, neurodevelopmental delay has been observed in few case reports describing a pattern of congenital anomalies in children exposed to MMI in utero (Greenberg, '87; Shikii et al., '89; Wilson et al., '98; Clementi et al., '99).

### SUMMARY

Antithyroid drugs are the treatment of choice for thyrotoxicosis in pregnancy. They do not represent major human teratogens. Data is insufficient to draw a definitive conclusion as to the teratogenic potential of MMI and CMZ. There are no prospective controlled studies supporting the teratogenicity of MMI. A cluster of case reports of ACC in association with prenatal MMI exposure suggests a probable weak association. They may be a result of a reporting bias. Controlled cohort studies will probably not give an answer because, for rare anomalies, their sample size may be inadequate. A case-control study comparing the incidence of ACC among offspring of women treated with MMI in pregnancy compared to another rare anomaly may provide an answer. A comparative study of the incidence of ACC among infants of women treated in pregnancy with MMI vs. PTU may further help. A rare

MMI embryopathy has been suggested in the literature. The evidence is yet insufficient to substantiate a causal relationship.

PTU has not been implicated in increasing the rate of major malformations in most studies. It may be advantageous over MMI or CMZ in pregnancy due to the lack of an association between PTU and ACC or an embryopathy, even if placental transfer of both drugs is similar.

With all antithyroid drugs, if used after the 10th gestational week, fetal toxicity should be looked for. Congenital goiter, thyroid dysfunction, or both occasionally occur. The risk is probably minimal after maternal treatment with MMI or CMZ and small after PTU, but prospective studies are still needed for a true risk estimate. In most cases, the effect is transient, and resolves spontaneously. Infants are at increased risk for hyperthyroidism due to placental transfer of thyroid stimulating immunoglobulins, as well as for hypothyroidism and goiter due to a direct drug effect. Prenatal ultrasonographic assessment of fetal thyroid gland is advised in women who are treated with antithyroid drugs during pregnancy. Invasive procedures should be considered in cases of significant enlargement of the thyroid gland or hydrops fetalis. Post natal assessment of neonatal thyroid function should be performed.

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