Birth defects observed with maternal carbimazole treatment: Six cases reported to Nice’s Pharmacovigilance Center

Malformations congénitales observées au cours d’un traitement maternel par carbimazole : six cas notifiés au Centre régional de pharmacovigilance de Nice

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Résumé

But. – Rapporter les cas d’embryopathies survenus après exposition aux antithyroïdiens de synthèse en début de grossesse. Méthodes. – Étude rétrospective des cas du registre de notre centre de pharmacovigilance depuis 1987. Résultats. – Nous rapportons six cas de malformations congénitales, toutes sous carbimazole, après exposition maternelle au cours du premier trimestre : deux cas de malformation de la paroi abdominale, dont un avec dysmorphie faciale associée, une malformation digestive (persistence du canal omphalo-mésentérique), deux cas d’aplasia cutis, dont un associé à une dysmorphie faciale similaire, et une atrésie bilatérale des choanes, associée à une coarctation de l’aorte dans un contexte de diabète insulinodépendant mal équilibré. Quatre patientes sur cinq avec bilan thyroïdien documenté au premier trimestre étaient euthyroïdiennes. Il existait dans trois cas un contexte faisant suspecter une prédisposition génétique : deux fentes labiopalatines parentales et une consanguinité. L’évolution a été favorable dans tous les cas. Conclusion. – Nous souhaitons rappeler la potentielletératogénicité du carbimazole, probablement sur terrain génétique prédisposé. Nous suggérons que soient rapportées de manière exhaustive les anomalies congénitales survenant chez les enfants de femmes avec maladie de Basedow, qu’elles soient ou non traitées par antithyroïdiens de synthèse. Dans l’état actuel des connaissances, il est préférable de prescrire du propylthiouracile chez les femmes hyperthyroïdiennes souhaitant une grossesse. © 2010 Elsevier Masson SAS. Tous droits réservés.

Mots clés : Grossesse ; maladie de Basedow ; Carbimazole ; Anomalies congénitales ; Embryopathies

Abstract

Goals. – To report cases of embryopathy occurring following first trimester exposure to anti-thyroid drugs. Methods. – Retrospective screening of the database of our Pharmacovigilance Center from 1987 to date. Results. – We report six cases of embryopathy, all following carbimazole exposure during the first trimester: two cases of abdominal wall defect, including one associated with facial dysmorphia; one case of digestive malformation (patent omphalomesenteric duct); two cases of aplasia cutis including one with facial dysmorphism; one case of bilateral choanal atresia with aorta coarctation associated with poorly controlled insulin dependent diabetes. Four out of five patients were euthyroid with treatment during the first trimester. We found a context suggesting genetic predisposition to congenital malformation in three cases: two cases of parental cleft lip/palate, one case of consanguinity. Outcome was favorable in all cases. Conclusions. – We want to raise awareness about the potential teratogenicity of carbimazole, probably on a predisposed genetic background. We suggest better reporting of congenital anomalies in children of women with Graves’ disease, with or without in utero exposure to anti-thyroid drugs. In light of current literature, propylthiouracil should be the first line treatment for hyperthyroid women wishing a pregnancy. © 2010 Elsevier Masson SAS. All rights reserved.

Keywords: Pregnancy; Graves’ disease; Carbimazole; Birth defects; Embryopathy

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1. Introduction

Graves’ disease, an autoimmune disease that often affects young women of child bearing age, is observed in 0.1 to 0.4% of pregnancies [1]. After gestational diabetes, it is the most frequent endocrine disease in pregnant women. In France, anti-thyroid drugs are the first line treatment for Graves’ disease. However, the conditions of treatment have to be adjusted during pregnancy [1,2]. Indeed, anti-thyroid drugs cross the placenta [3], and thus lead to two different types of risks according to the term: an early teratogenic risk, and later in pregnancy a risk of fetal hypothyroidism. Two classes of drugs are available in France: derivatives of mercapto-imidazol, mainly carbimazole (CBZ), widely used, or its metabolite methimazole (MMI) only recently available in France, and the derivatives of thiouracil, mainly propylthiouracil (PTU). The effects on fetal thyroid are similar for both classes, but as of today, only CBZ or its metabolite MMI have been incriminated in possible teratogenic effects [2,4–6], and not PTU though it is widely used worldwide.

The occurrence of aplasia cutis congenita (ACC) after early in utero exposure to MMI was first anecdotally reported in the 1970s, isolated or in association with another malformation [7,8]. But it was only at the end of the 1980s that the description of other malformations, some serious such as choanal and/or esophageal atresia, led to the concept of MMI/CBZ embryopathy [9,4,10,11,12,13,14,15]. This risk, that seems quite small (less than one per 1000 or even one per 10000 according to Cooper and Mandel [16], but up to 1% according to Di Gianantonio et al. [17]), and linked to very early exposure, would be specific of the imidazol class. However, the debate has been and remains quite heated [10,16,18], some authors implicating hyperthyroidism per se as well into this teratogenic risk [19,20,21], or warning against the assumed safety of PTU [22,23].

In France, the Reference Center for Teratogenic Agents collects national cases reported by the Regional Centers of Pharmacovigilance. Nationwide, only 30 or so cases have been reported since 1990, but the true incidence is likely to be underestimated, due to lack of coordination between endocrinologists, gynecologists, echographists and pediatricians. We present here six cases of congenital malformations reported to the Regional Center of Pharmacovigilance of Nice, in patients treated by CBZ during pregnancy.

2. Patients and Methods

We have reviewed prospectively all cases of embryopathy reported after in utero exposure to anti-thyroid drugs since the opening of the Pharmacovigilance Center in Nice in 1983. Six files were found. We reviewed the charts in detail, or when not available, the index card that was filled when the case was reported. We collected the following information: main type of malformation, associated malformation, outcome, term at birth and delivery mode, birth weight, detailed history of exposure (term, dosage, other associated drugs), information on the mother: age, gynecological and medical history, personal and familial malformation history, history of malformation on the paternal side.

3. Results

We report two cases of abdominal wall defect, one case of digestive malformation, two aplasia cutis and one bilateral choanal atresia (Table 1). In all cases, CBZ had been prescribed for maternal Graves’ disease.

The first case was a baby girl born in 1987 with a gastrochisis (or laparoschisis). Her mother, aged 25, G3P2 (another child normal, one miscarriage), non-smoker, received several other drugs for a psychiatric background. There was a family history of cleft lip/palate in her husband’s family (his father and sister). Graves’ disease was diagnosed at 7 weeks of amenorrhea (WA), with major thyrotoxicosis (fT4 62.9 pmol/l, fT3 34.2 pmol/l). Treatment by CBZ was immediately started at the dosage of 15 mg/day, then increased to 25 mg/day at 8 WA during a week. At 9 WA, the woman, wishing to abort, ingested 45 mg of CBZ. She later decided to continue the pregnancy, and the dosage was decreased to 15 mg until 12 WA. As fT4 fell into the normal range, dosage of CBZ was reduced to 10 mg/day until 14 WA, and to 5 mg/day until delivery. The baby girl, born by C-section at 37 WA + 5 days, had a severe gastrochisis with evisceration of the intestine, spleen and stomach, detected on prenatal ultrasound at 15 WA. She was born euthyroid, without goiter. After intubation and ventilation, the baby underwent two-phase complete surgical closure of the abdominal wall. The outcome was good.

The second case was a boy born with an omphalocele from a G2P2 (another child normal) mother with a known history of Graves’ disease. CBZ treatment was ongoing at onset of pregnancy (45 mg/day until 9 WA) associated with LT3 (Cynomel® 1 tablet/day), and was continued throughout pregnancy at decreasing dosage: 25 mg/day from 9 to 22 WA, 10 mg/day from 22 to 26 WA, and then 5 mg/day from 26 WA until delivery. The thyroid status during the first trimester is unknown. The boy, born vaginally at 37 WA, presented with a severe omphalocele with a right ureterocele diagnosed by antenatal ultrasound. He underwent successful multiple-step surgery. There were also dysmorphic facial features with small bilateral eyelid slits and a hypoplasia of nasal cartilage. The karyotype was normal.

The third case was a boy presenting with a patent vitello-intestinal duct, born to consanguineous parents (first cousins) from Maghrebian ancestry (39-year-old mother, 60-year-old father). The mother, non-smoker, G8P5 (four other children normal, two miscarriages, one abortion) was treated in October 2006 by CBZ 60 mg/day for Graves’ disease. She was then lost for follow-up, continued her treatment with CBZ at the same dosage, and presented again at 16 WA with a developing pregnancy. She was euthyroid (fT4 12.7 pmol/l, TSH 1.76 mUI/l, with borderline positive anti-TSH receptor antibodies 1.6 UI/l). Dosage of CBZ was immediately decreased to 10 mg/day, then 5 mg/day until delivery. The boy, delivered vaginally at 36 WA + 3 days, presented with a patent vitello-intestinal duct and ileo-umbilical fistula. A high arched palate was also noted. After a successful surgical treatment at 12 h of life, the immediate outcome was favorable; but on Day 9, there was a disjunction of the intestinal anastomosis, requiring a temporary ileostomy then...
Table 1
Birth defects reported following carbimazole treatment during pregnancy (CRPV Nice).

Malformations notifiées sous carbimazole (CRPV Nice).

<table>
<thead>
<tr>
<th>Case</th>
<th>Main malformation</th>
<th>Other anomalies</th>
<th>Maternal age (years)</th>
<th>Indication CBZ</th>
<th>Social/psy context</th>
<th>Maternal history</th>
<th>CBZ dosage</th>
<th>During 1st trimester</th>
<th>Thyroid results during 1st trimester</th>
<th>Other treatments</th>
<th>Birth weight (g)</th>
<th>Term and delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1987&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Laparoschisis</td>
<td>–</td>
<td>25</td>
<td>Diagnosis of Graves’ disease at 7 WA</td>
<td>Psychiatric context</td>
<td>Clef lip/palate on father’s side</td>
<td>7–8 WA: 15 mg/d&lt;sup&gt;c&lt;/sup&gt;</td>
<td>8–9 WA: 25 mg/d&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Hyperthyroid</td>
<td>Psychotropes + Avlocardyl&lt;sup&gt;®&lt;/sup&gt;</td>
<td>2800</td>
<td>37 SA + 5 d/C section</td>
</tr>
<tr>
<td>1990&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Omphalocele</td>
<td>Antenatal diagnosis</td>
<td>39</td>
<td>Preexisting Graves’ disease</td>
<td>–</td>
<td>–</td>
<td>0–9 WA: 45 mg/d + T3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>9–22 WA: 25 mg/d + T3</td>
<td>–</td>
<td>No</td>
<td>2765</td>
<td>37 WA/vaginal</td>
</tr>
<tr>
<td>2007&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Persistent omphalo-mesenteric duct</td>
<td>Facial dysmorphism: Hypoplasia of the nasal cartilage Upslanting palpebral fissures Right ureterocele</td>
<td>–</td>
<td>Preexisting Graves’ disease</td>
<td>Consanguinity</td>
<td>1 miscarriage</td>
<td>0–9 WA: 60 mg/d + LT4&lt;sup&gt;c&lt;/sup&gt;</td>
<td>9–19 WA: 20 mg/d + LT4</td>
<td>Euthyroid</td>
<td>–</td>
<td>2600</td>
<td>36 WA + 3 d/vaginal</td>
</tr>
<tr>
<td>2002&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Aplasia cutis</td>
<td>High arched palate</td>
<td>–</td>
<td>Preexisting Graves’ disease</td>
<td>–</td>
<td>–</td>
<td>0–10 WA: 20 mg/d&lt;sup&gt;c&lt;/sup&gt;</td>
<td>9–19 WA: 20 mg/d + LT4</td>
<td>–</td>
<td>?</td>
<td>2020</td>
<td>34 WA/C section</td>
</tr>
<tr>
<td>2004&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Aplasia Cutis</td>
<td>Facial dysmorphism, anomalous ear helice</td>
<td>–</td>
<td>Preexisting Graves’ disease</td>
<td>Psychiatric context</td>
<td>–</td>
<td>0–3 WA: 50 mg/d + T4&lt;sup&gt;c&lt;/sup&gt;, 3–8 WA: 20 mg/d&lt;sup&gt;c&lt;/sup&gt;, 8–23 WA: 5 mg&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Clef lip/palate</td>
<td>Psychosocial context</td>
<td>3160</td>
<td>38 WA/vaginal</td>
<td></td>
</tr>
<tr>
<td>2002&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Choanal atresia</td>
<td>Coarctation of the aorta</td>
<td>36</td>
<td>Preexisting Graves’ disease</td>
<td>Poorly controlled insulin dependent diabetes</td>
<td>–</td>
<td>0–13 WA: 60 mg/d + T3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>–</td>
<td>Insulin mix 25 and mix 50</td>
<td>2900</td>
<td>37WA + 3 d/vaginal</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Infant gender.
<sup>b</sup> Year of birth.
<sup>c</sup> CBZ dose during assumed period of susceptibility.
secondary reconnection on Day 21. Subsequent outcome was good.

The fourth case, reported by colleagues from Toulon, was an ACC discovered at birth in a baby girl born to a mother treated by CBZ for Graves’ disease since before pregnancy, at a dosage of 20 mg/day during the first 10 WA, together with levothyroxine (LT4). Treatment was then stopped. The child, delivered by C-section at 34 WA (because of a retro-placental hematoma), presented with localized alopecia and ACC measuring 3 cm, associated with dysmorphic facial features and malformation of the ears. The karyotype was normal.

The fifth case was an ACC occurring in a boy delivered vaginally at 38 WA. His 36-year-old mother, G2P2 (another child normal), had a personal history of cleft lip and palate, and a context of anxiety and depression. She had been treated for Graves’ disease for a year when she discontinued her contraceptive pill without informing her doctor; she became pregnant while taking 50 mg/day of CBZ and 112.5 mcg/day of LT4. As soon as pregnancy was recognized (3 WA), CBZ dosage was decreased to 20 mg/day and LT4 was discontinued. CBZ was then reduced further to 5 mg/day from 8 to 23 WA, and to 2.5 mg until delivery. The patient was euthyroid throughout pregnancy: 1 WA, fT4 16 pmol/l, TSH 0.02 mUI/l; 6 WA, fT4 7.5 pmol/l, TSH 0.99; 11 WA, fT4 17.9 pmol/l, TSH 0.01 mUI/l, slightly positive anti-TSH receptor at the threshold of positivity (9 UI/l, while 8.8%, fT4 18.3 pmol/l, f T3 6.6 pmol/l, TSH 0.03 mUI/l and anti-TSH receptor at the threshold of positivity (9 UI/l, while they were 310 UI/l 6 months earlier). CBZ dosage was then reduced to 20 mg/day and LT3 discontinued; at 22 WA, CBZ was decreased further to 10 mg until 26 WA, then stopped. After vaginal delivery at 37 WA + 3 days, the baby presented with respiratory distress and was transferred to intensive care. She was ventilated via a mouth tube, and a CT scan confirmed the diagnosis of bilateral choanal atresia with both bony and membranous involvement. The outcome was favorable after a two-phase surgical perforation of the choanae. Search for associated malformations detected a mild aortic coartation requiring no specific treatment.

4. Discussion

4.1. Experimental clues of CBZ/MMI teratogenicity

There are experimental clues showing a species-specific teratogenic effect of MMI, mainly in rats, though at concentrations higher than those used to treat hyperthyroid women [24]. This teratogenic effect does not seem to apply to PTU. However, some studies call for vigilance [22]; indeed, a study of “structure-activity” relationship of CBZ, MMI and PTU, in order to predict their developmental toxicity, has shown that the three molecules share structural fragments with teratogenic potential. Furthermore, the known higher liver toxicity of PTU [23] has been emphasized recently by a document from the Food and Drug Administration reporting cases of fetal hepatotoxicity when the mothers were treated with PTU [22].

Last, Stanisstreet et al. found a teratogenicity similar to MMI for ethylene thiourea (ETU), another compound with anti-thyroid effect [24]. This chemical, which shares structural analogy with MMI and PTU [25], can induce omphalocele and/or umbilical hernia as well as imperforated anus in rats [26]. However, in a recent literature review [25], there were no specific papers linking “classical” anti-thyroid drugs with abdominal wall defect.

4.2. Congenital malformations in humans

The six cases we are reporting are congenital malformations already described after in utero exposure to CBZ/MMI, suggesting maternal treatment with CBZ could be implicated. In humans, congenital malformations reported to date have not concerned PTU, excepting two cases reported by Mujtaba and Burrow [8], one hypospadias and one imperforated anus after PTU treatment, but likely without a causal link. This is true also in our series (six cases after CBZ exposure, none with PTU), though this could reflect treatment habits in our area before the specific recommendations for treatment during pregnancy, and also drug availability (until 2009, PTU was available in France only from hospital pharmacies).

4.2.1. Aplasia cutis congenita (ACC)

ACC is a rare, usually sporadic, malformation, affecting three out of 10,000 newborns [27]. It is defined as a skin defect of variable size on any area of the body, but mostly the scalp (70%). The lesion, unique in 75% of cases, is usually not a serious concern, unless it is associated with an underlying bone defect, which changes the therapeutic strategy, based on early plastic surgery. This defect is associated with other congenital malformations in only 8% of cases, though in our series, dysmorphic facial features were found in one of our two cases. Among the potential causes, the role of exposure to CBZ/MMI is widely accepted [6], despite the absence of maternal exposure to CBZ/MMI in one study of cases of ACC [27]. Since its first description in 1972 [7], ACC has been the most frequently reported malformation following in utero exposure to CBZ/MMI [8,9,18,28–39]. An original study indirectly incriminated MMI, showing a geographic and temporal association between the increased incidence of human ACC in specific areas of Spain and some veterinarian practices in the years 1980–1990 using MMI as an animal growth factor [40]. Because of other potential risk factors [5], an exhaustive history of exposure is necessary. Of note, the window of exposure is not clearly defined, but could extend from conception to 19 WA. In our two cases, exposure
was during early pregnancy, before 10 WA, but Iwayama et al. reports a case after exposure to CBZ between the 11th and the 17th weeks of gestation (13–19WA) [39]. Furthermore, some embryos had first been exposed to CBZ, until 6 WA for Baid and Merke [38] and 8 WA for Karg et al. [35], before being exposed to PTU (following the treatment switch), raising the question of causal attribution between the two compounds.

4.2.2. **CBZ/MMI embryopathy**

This concept proposed by Clementi et al. [4] encompasses several malformations, which are rather suggestive when associated: choanal and/or esophageal atresia, dysmorphic syndrome, growth or developmental delay. However, the teratogenic risk of CBZ/MMI, which seems restricted to the first 7 weeks of gestation [41], remains controversial for some [42] and so small for others (one for 1000 to one for 10,000) that treatment of maternal hyperthyroidism should not be questioned [16]. Some studies are negative, with no malformations found in the offspring of exposed mothers [17,19,43], but they often lack statistical power since those malformations are rare and the teratogenic effect is small. Indeed, a cohort study published in 2001 failed to find a statistically increased incidence of congenital malformations in 241 children exposed to MMI between the third and the seventh weeks of gestation compared to 1089 controls; however, the occurrence of one case of choanal atresia and one case of esophageal atresia in two babies exposed to MMI was considered, in that context, suggestive of a teratogenic effect of MMI [17].

4.2.2.1. **Choanal atresia**. Choanal atresia, a serious congenital malformation, affects about one out of 10,000 newborns. It can be uni- or bilateral, involving bony and/or membraneous choanae. It is syndromic in 50 to 75% of cases, often part of a specific genetic entity, such as CHARGE syndrome [13,20,64]. Since its first description in 1987 [9], it has been reported several times after maternal treatment with MMI/CBZ [4,11,13,15,20,41,44–48], and is usually associated with other malformations. More recently, a case-control study [20] has found a significant link between maternal treatment with MMI during pregnancy and the occurrence of choanal atresia, with an odds ratio of 17.65 [3.49–121.4]. However, the authors fuel the controversy, suggesting that it is maternal hyperthyroidism *per se* rather than MMI treatment that is responsible for such association, based on the period of exposure. Indeed, for some, the window of susceptibility is between the 7th and 8th WA, time of the formation of the primitive choanae; for others, it is later, between the 11th and 12th WA, at the time of the formation of the definitive choanae. However, the precise determination of that window is of paramount importance in order to incriminate a teratogenic agent. Indeed, it appears that several of the published cases of exposure to CBZ/MMI covered only the earlier period [4,12,17,18], with even in some cases [4,18] a secondary switch to PTU, which covered the later period, raising the question of remnant MMI in the body and even of the teratogenicity of PTU. Last, we should stress that, if a bilateral atresia cannot be missed because of the neonatal respiratory distress, it is possible that unilateral cases such as those reported by Lim et al. [49] and Myers and Reardon [11] are in fact more frequent and overlooked at birth, warranting systematic screening later in childhood. Our case of choanal atresia was associated with mild aortic coarctation, a cardiac malformation that has not been reported to our knowledge after CBZ/MMI exposure. Other cardiac malformations have been reported: transposition of the great arteries [50], ventricular septum defect [20,44,45,51] or patent ductus arteriosis [49]. The mother of our case also had poorly controlled insulin dependent diabetes that predisposes the fetus to cardiovascular malformations; however, aortic coarctation is not classical in that context [52]. Risk factors for a congenital aortic coarctation are not well elucidated, but many factors of the intra-uterine environment, including exposure to toxic factors, are suspected [53]. Thus, in our case, there are no formal clues linking the occurrence of the coarctation to the CBZ exposure or to the diabetes.

4.2.2.2. **Anomalies of the abdominal wall closure**. Anomalies of the abdominal wall closure, omphalocele and gastroschisis have also been found associated with *in utero* exposure to CBZ/MMI [10,18,54], with however only five cases reported so far to our knowledge, including two associated with ACC [54]. We report here two more cases, including one associated with dysmorphic facial features.

Omphalocele is due to an aplasia of the anterior abdominal wall at the level of umbilical cord implantation; its frequency in France is estimated between 3.9 for 10,000 births in Paris area [55] and 2.2 for 10,000 births in Alsace [56]. This serious anomaly of embryogenesis, with intestinal loops covered by a sac, is usually associated with other malformations and with chromosomal anomalies, suggesting a genetic predisposition. The window of susceptibility is estimated between the 6th and 8th WA.

Gastroschisis is also due to an aplasia of the anterior abdominal wall, but usually localized on the right side of the implantation of the umbilical cord (which is normal), with a spilling out of the intestinal loops freely exposed to amniotic fluid, without a protective sac. Its prevalence in France is 1.8 [56] to 1.9 [57] for 10,000 births. It has a better prognosis and is usually isolated, without chromosomal anomaly; it could be due to an involution of the right umbilical vein. The period of susceptibility is estimated between the 7th and 8th WA, period of the initiation of CBZ therapy in our case.

Those malformations are serious, with an overall survival rate of 63.8% for the babies born with gastroschisis and of only 24.1% for those with an omphalocele, according to a French study [56]. Detection is possible on antenatal ultrasound studies after 12 WA (two cases out of two in our series), leading to a safer delivery, usually by C-section to avoid trauma of the intestinal loops, and enabling scheduled neonatal surgery.

4.2.2.3. **Anomalies of the vitello-intestinal duct**. Anomalies of the vitello-intestinal duct are gastrointestinal tract malformations occurring in 2% of newborn, ranging from the quite frequent simple Meckel’s diverticulum up to the complete persistence of the omphalo-mesenteric duct, which is much rarer and more serious because of the risk of stercoral peritonitis [57]. Six
cases of patent vitello-intestinal duct have been reported so far in relation to maternal treatment with MMI/CBZ [12,15,29,44,58]. We report here one more case associated with a high arched palate. This anomaly can be mistaken for a wall defect, as in the case reported by Ono et al. [57], where prenatal ultrasound and MRI studies were more suggestive of gastroschisis.

In our series, there was neither esophageal atresia nor tracheoesophageal fistula, which are part of the “classical” CBZ/MMI embryopathy [4,10,44,51,59]. There was no nipple anomaly recorded either (athelia, hypothelia, or supernumerary nipple) that have often been described in association with other malformations [9,11–13,20,34,45]. But we found in two cases facial dysmorphic features similar to the other cases described in the literature [4,9,11–14,18,20,41,45,48,51,60]: small, upslanting palpebral fissures, hypoplasia of nasal cartilage and anomalies of the ear helices. Facial and nipple malformations can be easily overlooked when minor, and thus should be systematically screened for in exposed babies.

Other anomalies have been reported in babies exposed to CBZ/MMI at the beginning of pregnancy. This is neither surprising nor specific, as congenital malformations affect in France 3.2% of newborns [55], and thus can occur by chance in the offspring of women treated by CBZ/MMI. For some anomalies, recurrent and/or associated to ACC or choanal atresia, the responsibility of CBZ/MMI is plausible; for others it could be mere coincidence. Have been described: biliary tree atresia [59]; cardiac malformations [20,44,49,50,51], iridic and retinal colobomas [58,60]; dystrophic fingernails [34]; patent urachus [7]; syndactylies [34]; radio-cubital synostosis [14]; Potter syndrome (bilateral kidney agenesis [61]); and even an ectasia of renal pelvis [60] or a hypogonadotrophic hypogonadism [12]. Regarding mental delay [4,9,14,45], it could be multifactorial, secondary to fetal hypothyroidism, premature birth, or even an associated chromosomal defect.

Usually, the prognosis depends on the severity of the malformation and the premature birth. Unfortunately, seven deaths have been reported among the 37 cases of well-documented polynamformations [10,44,49,50,51,54,58].

4.3. Physio-pathological mechanisms of malformations

4.3.1. Interactions between genetic background and environment

Out of our six cases, we found once a parental consanguinity and twice a history of familial history of cleft palate/lip (in the mother or in the paternal family), which could suggest a genetic predisposition for congenital malformations [62,63]. A detailed family history of congenital malformations should be taken to assess more precisely this risk. Of note, however, though cleft palate/lip are more often associated to other congenital anomalies, it does not seem to be associated to abdominal wall defects or choanal atresia [63].

The type of malformations involved can be found outside the context of exposure to teratogenic compounds, and genetic causes have been identified in some cases. For example, the CHARGE syndrome, which associates coloboma, cardiac malformation, choanal atresia, growth and developmental delay, genital and ear anomalies [64], is linked to mutations in CHD7 gene. Another syndromic embryopathy combining three anomalies, including choanal atresia, and hypothelia/athelia has also been reported recently in a consanguineous Palestinian family [65] in the absence of drug exposure. This could lead to the hypothesis that some genetic susceptibility could be unmasked by the exposure to a teratogen, in this case CBZ/MMI [12].

Last, recently has been shown an association of gastroschisis with a polymorphism of genes implicated in angiogenesis, those genes strongly interacting with maternal smoking [66]. Some drugs taken by the mothers of children with abdominal wall defects have also been identified as risk factors [56]. For example, Torfs et al. in 1996 has shown in a case-controls study (110 cases, 220 controls) that gastroschisis was associated with the mother taking aspirin, ibuprofen or two nasal decongestants, though not with anti-thyroid drugs [67]. This suggests the role of environmental factors on a specific genetic background.

4.3.2. The role of hyperthyroidism

One hypothesis regarding the potential benefit of PTU compared to CBZ/MMI rests on the pharmacological action of PTU that, as opposed to CBZ/MMI, is able to inhibit type 1 deiodinase, the enzyme that transforms T4 into T3. The accumulation of T3 in fetuses of mothers not treated by PTU could, for some, generate the malformations observed with CBZ/MMI [20], thus in keeping with the hormonal hypothesis of a teratogenic effect of hyperthyroidism per se [19–21,59]. But for Lian et al. [21], there was still an increased risk of malformation with MMI compared to PTU (five out of 12 cases versus one out of 61 cases). Of note, out of the five patients of our series for whom thyroid tests are available during the first trimester of pregnancy, only one was hyperthyroid, the four others being euthyroid. But those thyroid tests are only a snapshot at a given time, and it is difficult to extrapolate to the whole period of embryogenesis.

4.3.3. Absence of dose-effect

Regarding a potential role of the dosage, the literature is rather scarce; however, malformations have been observed at very low dosages, such as 5 mg MMI in one of the cases reported by Barbero et al. [20]. In our series, exposure was average to high (15–60 mg of CBZ), reflecting therapeutic practices in non pregnant women. No threshold for teratogenic effect is currently proposed.

4.4. Therapeutic recommendations

There is currently a consensus for treating maternal Graves’ disease in order to decrease the risk of miscarriage and maternal and fetal complications [1,2]. The therapeutic goals for the first trimester, when the fetal thyroid is not yet functioning, is to control maternal thyroid function with the lowest dosage of antithyroid drug possible, and to minimize the risks of embryopathy [1,2,6].

Thus, current recommendations are, as a precautionary measure, to avoid MMI/CBZ at the beginning of pregnancy, and even ideally to replace CBZ by PTU during the pre-conception period, CBZ or MMI being reserved for the cases of allergies or
failure of PTU, as proposed in the French physician’s drug reference book (the Vidal). Indeed, when the diagnosis of pregnancy is made, the period of the maximum risks for malformations is often over. Thus, as for diabetes, pregnancy should be planned, and the questions relating to the date of the last menstrual cycle, contraception, and/or desire for pregnancy should be brought up at the first visit, and at all the following visits. This will lead to the prescription of an effective contraception if a pregnancy is not desired within the next 18 months, or to propose a treatment by PTU if a pregnancy is envisaged, with a therapeutic schema targeting fT4 at the upper limit of normal, without supplementation with thyroid hormones. If a pregnancy occurs in a woman taking CBZ, the switch to PTU is warranted if the woman is seen very early. Beyond 10 WA, it is reasonable to reassure her, as the teratogenic risk is low. In all cases, fetal ultrasound follow-up by an informed specialist will focus particularly on the detection of embryopathy, allowing, if needed, to plan ahead for neonatal care. In agreement with Cooper and Mandel [16], and at odds with Karlsson et al. [10], those recommendations, in our views, should not prevent the prescription of CBZ or MMI in a young woman with no desire for pregnancy. Indeed, CBZ/MMI is better tolerated with less side effects, particularly hepatic effects [68], the dosages are lower than PTU, in addition to easier use (only one dose a day).

5. Conclusion

Our retrospective series of six cases should draw the attention of prescribing doctors to the risks of congenital malformations associated with the treatment of hyperthyroidism during pregnancy. The causal effect of CBZ/MMI in the occurrence of ACC is well established, although certain unknowns persist regarding the association with other malformations, illustrating the complex interactions between genetic background and fetal environment, both endo- and exogenously. The lack of solid data should trigger prospective studies based on the systematic report of any congenital anomalies in children of women with Graves’ disease, whether treated or not, noting all treatments taken, periods of exposure, family history of congenital malformations and other maternal diseases. A multidisciplinary approach should allow a more precise assessment of the incidence of this embryopathy.

The new recommendations for the treatment of Graves’ disease in pregnancy and wider access to PTU, now available in pharmacies in France, will greatly increase the number of women (and their embryos) exposed to PTU during the first trimester. This change in the therapeutic approach should be closely monitored to confirm or not the expected benefit.

Conflict of interest statement

None.

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