Antithyroid Drugs and Congenital Heart Defects: Ventricular Septal Defect (VSD) is part of the Methimazole/Carbimazole embryopathy

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Children born to mothers with Graves’ disease require careful attention from obstetricians and pediatricians. In a new publication by Besancon et al (1), the authors focused on the thyroid function and clinical outcomes of 68 neonates born to mothers with past or present Graves’ disease. The study draws important conclusions on the management of neonatal thyroid function at birth and in the postnatal period, and it emphasizes the role of maternal TSH receptor antibodies (TRAb) status in late pregnancy (1). Thus, focus must be on both the mother and the child in the management of pregnant women with Graves’ disease (2).

The study by Besancon et al (1) also draws attention to another important aspect in the management of children born to mothers with Graves’ disease; the risk of birth defects. Echocardiography was performed in 60 of the 68 neonates, and four cases of congenital heart defects (CHDs) compatible with a diagnosis of birth defect according to the 10th revision of the International Classification of Disease (ICD-10) were reported including two atrial septal defects (ASD), one ventricular septal defect (VSD) and one tetralogy of Fallot (1). In addition to this, one case of congenital pulmonary airway malformation and one case of aplasia cutis were described, but it is not clear how and when non-cardiac birth defects were diagnosed. Considering their findings, the authors state that ‘a possible link between antithyroid drug (ATD) therapy and cardiac malformations is unclear and needs to be ascertained in larger databases’ (1).

The association between the use of ATD in pregnancy and birth defects has been considered for years, and the first report consisting of 13 lines was published in 1972 (3). In this letter, the authors described cases of aplasia cutis in children born to mothers who had been treated with Methimazole in the pregnancy. Many case reports were subsequently published, and they often described the same types of severe birth defects combined in the term ‘Methimazole/Carbimazole embryopathy’ (facial dysmorphism, aplasia cutis, choanal atresia, esophageal atresia, and omphalomesenteric anomalies) (4). During the last decade the association between the use of ATD and birth defects has also been ascertained in larger databases. We performed a Danish nationwide cohort study of all children live-born in Denmark from 1996 to 2008 (n=817,093) (5). Methimazole/Carbimazole
(MMI/CMZ) treatment in early pregnancy (up to and including gestational week 10) was associated with an increased prevalence of birth defects diagnosed before the age of two years (3.4% additional cases) and this included an increased risk of congenital heart defects (CHDs) (5).

CHDs are the most common major birth defect (www.eurocat-network.eu /accessprevalencedata/prevalencetables, accessed on June 23, 2014), and ventricular septal defect (VSD) is the most prevalent CHD (6). CHDs are often detected within the first year of life, but some defects e.g. defects of cardiac septa may be asymptomatic (6, 7). Looking into details on CHDs and the use of ATD in early pregnancy, we followed 1,097 children exposed to MMI/CMZ in early pregnancy and 811,730 non-exposed children from birth to a diagnosis of CHD, emigration, death or December 31, 2010 whichever came first (to median age 8.3 years), using methods previously described in detail (8). As depicted in the upper part of Figure 1, the overall frequency of CHDs was higher in children exposed to MMI/CMZ (adjusted hazard ratio (aHR) versus non-exposed: 1.84 (95% confidence interval (CI) 1.26-2.68). Considering subgroups of CHDs, only defects of cardiac septa revealed a significant association with MMI/CMZ (aHR 1.87 (95% CI 1.14-3.05). Compared with non-exposed children (lower part of Figure 1), there was a significantly higher prevalence of VSD alone and a diagnosis of both VSD and ASD in MMI/CMZ exposed children.

Results suggest that the use of MMI/CMZ in early pregnancy is associated with an increased risk of VSD (and possibly also ASD). Embryonic development of the atrial and ventricular septa begins in the middle of gestational week 6 (calculated from the first day of the last menstrual period) and is completed by the end of gestational week 10 (9). Thus, development takes place within the period of early pregnancy ATD exposure defined in our study (8), and our finding is also in line with published individual case reports; minimum six cases of VSD have been described in children born to mothers treated with MMI/CMZ in early pregnancy (10-15). In five cases, the child also had other birth defects belonging to the Methimazole/Carbimazole embryopathy (esophageal atresia, omphalocele, choanal atresia, facial dysmorphia). Similarly in our Danish study (5), three children...
with a diagnosis of VSD had such additional birth defects (esophageal atresia, omphalocele, aplasia cutis). Thus, evidence support that VSD is a part of the Methimazole/Carbimazole embryopathy. The clinical significance of such septum defects needs to be clarified in a study with longer follow-up time.

Besancon et al (1) reported one case of VSD and in addition to this, one case of aplasia cutis which is a ‘classical’ Methimazole/Carbimazole birth defect. The major period of organogenesis is the very early pregnancy (first trimester), and gestational week 6-10 is the period most sensitive to teratogenic exposure (16). However, maternal use of ATD in early pregnancy was not detailed in the report by Besancon et al. They focused on the late pregnancy (third trimester), and the pregnant women were included in the study at mean gestational week 17 (range week 10-28). When a clinical outcome such as birth defects is studied, it is imperative to have detailed information on exposure in early pregnancy. Information on ATD treatment and thyroid function in early pregnancy would be warranted to evaluate if the cases of birth defects described by Besancon et al could be associated with maternal ATD treatment.

Optimal management of pregnant women with Graves’ disease should start before pregnancy occurs and continue throughout pregnancy (16). Considering the neonate, evaluation of maternal TRAb status in the late pregnancy is important as emphasized in the study by Besancon et al (1). However, if the mother received ATD in early pregnancy, careful evaluation of the neonate for high risk birth defects is imperative (5).

**Conflict of interest**

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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pregnancy: focus on both maternal and foetal thyroid function, and caution against surgical

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**Legend to figure**

Prevalence of congenital heart defects in children exposed to Methimazole/Carbimazole (MMI/CMZ) in early pregnancy (n=1,097) and non-exposed children (n=811,730). The children were followed from birth to a median age of 8.3 years (range 0-15 years), as previously described (8). Among all congenital heart defects (DQ20-28), the subgroup ‘defects of cardiac septa’ (DQ21) was significantly associated with MMI/CMZ exposure (upper figure). Among defects of cardiac septa (lower figure), all MMI/CMZ exposed cases had a diagnosis of DQ210 (VSD; ventricular septal defect), DQ211 (ASD; atrial septal defect) or DQ212 (AVSD; atrioventricular septal defect). P-values are results of the Chi-square test: MMI/CMZ exposed versus non-exposed. NS; non-significant. DQ; diagnosis according to the 10th revision of the International Classification of Disease (ICD-10).
Figure 1

- Defects of cardiac septa (DQ21) p=0.011
- All congenital heart defects (DQ20-DQ28) p=0.002
- VSD alone (DQ210) p=0.013
- VSD and ASD (DQ210 + DQ211) p=0.003
- ASD alone (DQ211) NS
- AVSD (DQ212) NS