Antithyroid drugs and congenital heart defects: ventricular septal defect is part of the methimazole/carbimazole embryopathy

Stine Linding Andersen[1,2,3] and **Peter Laurberg**[1,2]

[1]Department of Endocrinology, Aalborg University Hospital, Sdr. Skovvej 15, 9000 Aalborg, Denmark, [2]Department of Clinical Medicine, Aalborg University, Aalborg, Denmark and [3]Department of Clinical Biochemistry, Aalborg University Hospital, Aalborg, Denmark

Correspondence should be addressed to S L Andersen
Email
stine.a@rn.dk

European Journal of Endocrinology

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 emphazises 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 dysmorphia, aplasia cutis, choanal atresia, oesophageal 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 2 years (3.4% additional cases) and this included an increased risk of CHDs (5).

CHDs are the most common major birth defect (www.eurocat-network.eu/accessprevalencedata/prevalencetables, accessed on June 23, 2014), and 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 now expanded our study and followed 1097 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

www.eje-online.org
DOI: 10.1530/EJE-14-0524

Published by Bioscientifica Ltd.

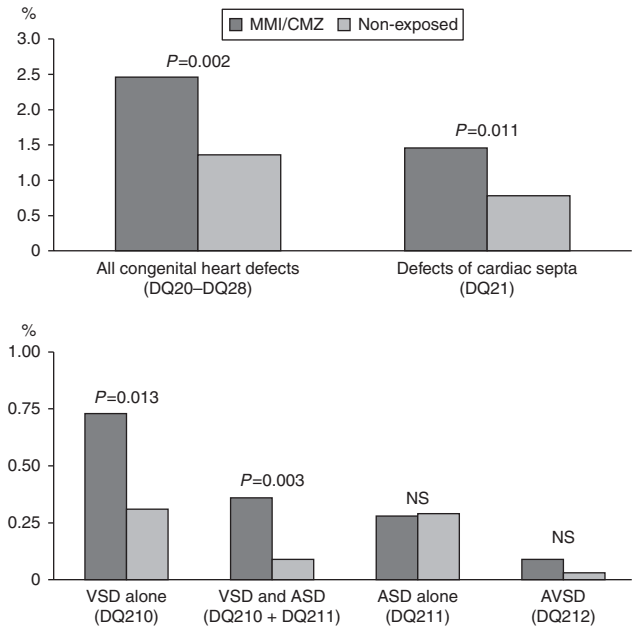

Figure 1

Prevalence of congenital heart defects in children exposed to methimazole/carbimazole (MMI/CMZ) in early pregnancy ($n = 1097$) 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 χ^2 test: MMI/CMZ exposed vs non-exposed. NS, non-significant. DQ; diagnosis according to the 10th revision of the International Classification of Disease (ICD-10).

in detail (8). As depicted in the upper part of Fig. 1, the overall frequency of CHDs was higher in children exposed to MMI/CMZ (adjusted hazard ratio (aHR) vs non-exposed: 1.84 (95% 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 Fig. 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 VSD in combination with 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; a minimum of six cases of VSD have been described in children born to mothers treated with MMI/CMZ in early pregnancy (10, 11, 12, 13, 14, 15). In five cases, the child also had other birth defects belonging to the MMI/CMZ embryopathy (oesophageal atresia, omphalocele, choanal atresia, facial dysmorphia). Similarly, in our Danish study (5), three children with a diagnosis of VSD had such additional birth defects (oesophageal atresia, omphalocele, aplasia cutis). Thus, evidence support that VSD is a part of the MMI/CMZ 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' MMI/CMZ 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 emphasised 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).

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

References

1 Besancon A, Beltrand J, Le Gac I, Luton D & Polak M. Management of neonates born to women with Graves' disease: a cohort study. *European Journal of Endocrinology* 2014 **170** 855–862. (doi:10.1530/EJE-13-0994)

2 Laurberg P, Bournaud C, Karmisholt J & Orgiazzi J. Management of Graves' hyperthyroidism in pregnancy: focus on both maternal and foetal thyroid function, and caution against surgical thyroidectomy in pregnancy. *European Journal of Endocrinology* 2009 **160** 1–8. (doi:10.1530/EJE-08-0663)

3 Milham SJ & Elledge W. Maternal methimazole and congenital defects in children. *Teratology* 1972 **5** 125–126. (doi:10.1002/tera.1420050117)

4 Foulds N, Walpole I, Elmslie F & Mansour S. Carbimazole embryopathy: an emerging phenotype. *American Journal of Medical Genetics. Part A* 2005 **132A** 130–135. (doi:10.1002/ajmg.a.30418)

5 Andersen SL, Olsen J, Wu CS & Laurberg P. Birth defects after early pregnancy use of antithyroid drugs: a Danish nationwide study. *Journal of Clinical Endocrinology and Metabolism* 2013 **98** 4373–4381. (doi:10.1210/jc.2013-2831)

6 Penny DJ & Vick GW. Ventricular septal defect. *Lancet* 2011 **377** 1103–1112. (doi:10.1016/S0140-6736(10)61339-6)

7 Geva T, Martins JD & Wald RM. Atrial septal defects. *Lancet* 2014 **383** 1921–1932. (doi:10.1016/S0140-6736(13)62145-5)

8 Andersen SL, Olsen J, Wu CS & Laurberg P. Severity of birth defects after propylthiouracil exposure in early pregnancy. *Thyroid* 2014. In press. (doi:10.1089/thy.2014.0150)

9 Moore KL, Persaud TVN & Torchia MG. Cardiovascular system. In *The Developing Human: Clinically Oriented Embryology*, 9th edn, ch 13, pp 289–342. Eds KL Moore, TVN Persaud & MG Torchia. Philadelphia: Saunders/Elsevier, 2013.

10 Ramirez A, Espinosa de los Monteros A, Parra A & De Leon B. Esophageal atresia and tracheoesophageal fistula in two infants born to hyperthyroid women receiving methimazole (Tapazol) during pregnancy. *American Journal of Medical Genetics* 1992 **44** 200–202. (doi:10.1002/ajmg.1320440216)

11 Johnsson E, Larsson G & Ljunggren M. Severe malformations in infant born to hyperthyroid woman on methimazole. *Lancet* 1997 **350** 1520. (doi:10.1016/S0140-6736(05)63942-6)

12 Di Gianantonio E, Schaefer C, Mastroiacovo PP, Cournot MP, Benedicenti F, Reuvers M, Occupati B, Robert E, Bellemin B, Addis A *et al*. Adverse effects of prenatal methimazole exposure. *Teratology* 2001 **64** 262–266. (doi:10.1002/tera.1072)

13 Karlsson FA, Axelsson O & Melhus H. Severe embryopathy and exposure to methimazole in early pregnancy. *Journal of Clinical Endocrinology and Metabolism* 2002 **87** 947–949. (doi:10.1210/jcem.87.2.8126)

14 Barbero P, Valdez R, Rodriguez H, Tiscornia C, Mansilla E, Allons A, Coll S & Liascovich R. Choanal atresia associated with maternal hyperthyroidism treated with methimazole: a case–control study. *American Journal of Medical Genetics. Part A* 2008 **146A** 2390–2395. (doi:10.1002/ajmg.a.32497)

15 Goel H & Dudding T. Carbimazole/methimazole embryopathy in siblings: a possible genetic susceptibility. *Birth Defects Research. Part A, Clinical and Molecular Teratology* 2013 **97** 755–758. (doi:10.1002/bdra.23200)

16 Laurberg P & Andersen SL. Antithyroid drug use in early pregnancy and birth defects. Time windows of relative safety and high risk? *European Journal of Endocrinology* 2014 **171** R13–R20. (doi:10.1530/EJE-14-0135)

Received 26 June 2014
Revised version received 21 July 2014
Accepted 28 July 2014