Q J Med 2012; **105**:189–193
doi:10.1093/qjmed/hcq248 Advance Access Publication 21 January 2011

Case report

QJM

Carbimazole embryopathy: implications for the choice of antithyroid drugs in pregnancy

P. BOWMAN[1], N.J. OSBORNE[1], R. STURLEY[2] and B. VAIDYA[3]

From the [1]Department of Paediatrics, [2]Department of Obstetrics and [3]Department of Endocrinology, Royal Devon and Exeter Hospital, Exeter, UK

Address correspondence to Dr P. Bowman, Bramble Ward, Royal Devon & Exeter Hospital, Barrack Road, Exeter EX2 5DW, UK. email: pamelabowman@nhs.net

Summary

Maternal thyrotoxicosis, predominantly secondary to Graves' disease, affects 0.2% of all pregnancies. The Endocrine Society guidelines recommend the use of propylthiouracil as a first-line drug for thyrotoxicosis in pregnancy because of associations between carbimazole or methimazole and congenital anomalies. However, recent studies have highlighted the risk of severe liver injury with propylthiouracil. Here, we report another case with multiple congenital anomalies following *in utero* exposure to carbimazole and review the literature to consider the risks and benefits of available pharmacological treatments for thyrotoxicosis in pregnancy.

Case report

Our case is a 1-year-old girl whose mother suffers from Graves' disease. The mother was taking carbimazole 40 mg with thyroxine 100 mcg daily at conception, which was unplanned. When it was discovered she was pregnant, the thyroxine was stopped and the carbimazole gradually reduced reaching 10 mg daily by term. The mother remained euthyroid throughout pregnancy.

The baby was born at 38 weeks gestation by forceps delivery due to fetal distress. Reassuringly, Apgar scores were 10 and 10 at 1 and 5 min, respectively, and routine post-natal examination on Day 1 was considered normal. Birth weight was 2.78 kg (10th centile). A high thyroid stimulating hormone of 13.8 mIU/l (screening cut-off 6 mU/l) was noted on routine biochemical (bloodspot) screening on Day 5 of life and the baby was seen in paediatric outpatient clinic for this reason. Her thyroid hormone levels normalized without intervention. However, it was noted that she had an atypical umbilical stump and further investigation identified a patent vitellointestinal duct which was surgically repaired at age 5 months. The baby was also found to have a scalp defect on the occipital region consistent with aplasia cutis (Figure 1A). Although she had no major facial dysmorphism, she had a large forehead, broad flat nasal bridge and thin upper lip (Figure 1B). She was investigated for persistent upper airway noise and fibreoptic nasendoscopy showed laryngomalacia but there was no evidence of choanal atresia. Barium swallow excluded oesophageal atresia and tracheo-oesophageal fistula. Of note, she also had normal hearing and normal developmental milestones.

Literature review

We conducted a review of the English literature in Medline. Search terms used were 'carbimazole, methimazole, propylthiouracil, birth defects, congenital anomalies, embryopathy, aplasia cutis.'

Figure 1. (**A**) Aplasia cutis of the scalp; (**B**) Facial appearance of the patient.

To support the concept of an embryopathy we included cases of two or more congenital anomalies appearing together in the same patient and excluded single defects seen in isolation as they would be more likely to have occurred by chance. Our literature review revealed 31 other cases with two or more congenital anomalies following *in utero* exposure to carbimazole or methimazole (Supplementary Table).

Discussion

Many of the anomalies identified in our patient have been reported before in babies exposed to carbimazole or methimazole antenatally. Scalp defects in babies of methimazole-treated mothers were first noted in 1972.[1] Since then there have been several other reports of scalp abnormalities including aplasia cutis in the literature. Aplasia cutis, the congenital absence or deficiency of a localized area of skin (usually on the scalp), is rare in babies not exposed to teratogens, with a birth prevalence of 0.03%.[2] Similarly, patency of the vitellointestinal duct is rare as an isolated birth defect, with a reported incidence of 0.0053%.[3] The vitellointestinal duct connects the midgut to the yolk sac in early embryonic life and failure of its obliteration at Weeks 5–6 of gestation leads to a fistula between the umbilicus and the ileum. Patent vitellointestinal duct has been reported before in babies of mothers who took carbimazole during pregnancy.[4–6] Our patient also had laryngomalacia, stridor caused by delay in development of the structures (epiglottis/arytenoids/aryepiglottic folds) supporting the larynx. There are no previous reports in the literature linking this with carbimazole/methimazole use. Given the associations reported between these drugs and choanal atresia,[5–14] and the anatomical proximity of the choanae and laryngeal structures, there is a possibility that the laryngomalacia is related to carbimazole therapy. However, as this is a far more common neonatal presentation than the other anomalies noted, it may have been a coincidental finding unrelated to drug treatment. Finally, we noted characteristic facial features including a large forehead, broad flat nasal bridge and thin upper lip. This is consistent with previous case reports of distinctive facies in these children.[5,7–13]

A summary of different congenital malformations reported in the 31 published cases of carbimazole embryopathy is shown in Table 1. The appearance of several otherwise rare defects together in the children exposed to carbimazole or methimazole, but not to propylthiouracil, *in utero* supports the concept of an embryopathy specific to this type of anti-thyroid drug. Perinatal mortality (4 out of 31 cases; 13%) and premature birth (12 out of 25 cases with data available; 48%) were common in these babies (Supplementary Table). The features of the embryopathy do not appear to be related to the dose of drug administered, and the majority of

Table 1 Prevalence of various congenital anomalies in previously reported cases (total $n = 31$) of carbimazole/methimazole embryopathy[a]

Systems	Congenital anomalies	Percentage
Skin	Aplasia cutis	29
Upper airways	Choanal atresia	65
	Tracheo-oesophageal fistula	13
Gastrointestinal	Patent vitello-intestinal duct	16
	Oesophageal atresia	13
	Omphalocele	6
	Others (e.g. imperforate anus, microcolon, umbilical hernia, gallbladder aplasia)	10
Cardiovascular	Ventricular septal defects	10
	Others (e.g. overriding aorta)	3
Others	Dysmorphic facies	68
	Nipple anomalies (e.g. athelia, hypoplastic nipples)	23
	Developmental delay	16
	Deafness	6
	Iris/retinal coloboma	6

[a]See Supplementary Table for details.

mothers were reported as being euthyroid during the pregnancy (Supplementary Table).

Carbimazole has historically been more widely used in the treatment of thyrotoxicosis in women of reproductive age or in pregnant women than propylthiouracil. This could have introduced bias in the reporting of individual cases of congenital anomalies related to carbimazole. A number of cohort studies have analysed the risk of congenital anomalies associated with the use of different anti-thyroid drugs in pregnancy. Two relatively small studies reported no difference in the number of major congenital anomalies seen in babies exposed to carbimazole/methimazole or propylthiouracil.[15,16] In contrast, a study from Sweden found four reports between 1995–2000 of infants born with oesophageal atresia and omphalocele or choanal atresia, three of whom had been exposed to methimazole in the first trimester; there was no association between these anomalies and propylthiouracil.[17] A recent case control study that included over 18 000 cases with congenital malformations, 127 of whom were exposed to anti-thyroid drugs in the first trimester, showed a significant association between *in utero* exposure of carbimazole/methimazole and choanal atresia or omphalocele.[18] *In utero* exposure to propylthiouracil was not associated with these congenital anomalies in this study, but there was a tentative suggestion of an association with situs inversus, renal and cardiac malformations.[18] Taken together, although causality cannot be directly proven, the association between carbimazole/methimazole and congenital malformations is strengthening.

It has been suggested that maternal thyrotoxicosis itself (and not the drugs used to treat it) has teratogenic effects on the fetus.[19] Gastrointestinal anomalies have been observed in babies of mothers with untreated hyperthyroidism in pregnancy.[20] Barbero *et al.*[19] reported a case of bilateral choanal atresia and branchial fistula in a child whose mother was diagnosed with hyperthyroidism in pregnancy and did not start methimazole treatment until 28 weeks' gestation.[19] However, it is noteworthy that most mothers of children with congenital anomalies following exposure to carbimazole/methimazole have been reported as euthyroid throughout pregnancy (Supplementary Table).

Both carbimazole/methimazole and propylthiouracil are equally effective in controlling thyrotoxicosis in pregnancy.[16] The most recent guidance from the Endocrine Society recommends the use of propylthiouracil as a first line drug, if available, especially during first trimester organogenesis, because of associations between carbimazole/methimazole and congenital anomalies.[21] Methimazole, and by implication, carbimazole, should be used only if propylthiouracil is not available or if the patient cannot tolerate or has an adverse response to propylthiouracil.[21] However, more recent works have raised concerns regarding the safety of propylthiouracil.[22] Severe hepatotoxicity resulting in liver transplantation and in some cases death has been reported in adults (including pregnant women) and children. Liver injury has also been reported in fetuses exposed to propylthiouracil in utero.[22] The US Food and Drug Administration issued a black box warning for propylthiouracil in 2009 that notified healthcare professionals of these risks.[23]

Further work is required to establish more clearly the optimum treatment regime for thyrotoxicosis in pregnancy. Based on available data, a pragmatic approach in a planned pregnancy is to use propylthiouracil just prior to conception and during the first trimester, thereby avoiding fetal carbimazole exposure during the critical time of organogenesis. The mother could then be treated with carbimazole from the second trimester throughout the remainder of the pregnancy, reducing the time of exposure of mother and fetus to the potentially hepatotoxic effects of propylthiouracil.[22] In addition, not all

pregnancies are planned and therefore all women with reproductive potential should be informed of the potential risk of teratogenicity when starting treatment with carbimazole/methimazole.

In conclusion, the constellation of several rare but distinctive congenital anomalies in this and other published cases supports the concept of a carbimazole embryopathy and the current guidelines that carbimazole should be avoided in the first trimester of pregnancy.

Notes added in proof

Since submission of our case-report, the patient was assessed for persistent right eye epiphora since birth, and was found to have congenital absence of both lower lacrimal punctae. Syringing and probing through right upper lacrimal punctum also revealed right nasolacrimal atresia, which was treated with insertion of a stent.

Supplementary data

Supplementary data are available at *QJMED* online.

Acknowledgements

We would like to acknowledge the parents of our case for kindly giving their consent to describe her clinical features in this report.

Funding

National Institute for Health Research (NIHR to B.V.); the views expressed in this publication are those of the authors and not necessarily those of the National Health Service, the NIHR or the Department of Health, UK.

Conflict of interest: None declared.

References

1. Milham S Jr, Elledge W. Maternal methimazole and congenital defects in children. *Teratology* 1972; **5**:125–6.
2. Van Dijke CP, Haydendael RJ, De Klein MJ. Methimazole, carbimazole and congenital skin defects. *Ann Intern Med* 1987; **106**:60–1.
3. Singh S, Pandey A, Ahmed I, Rawat JD, Sharma A, Srivastava NK. Prolapse of bowel via patent vitello intestinal duct—a rare occurrence. *Hernia* 2010 [Epub ahead of print; 17th June 2010; doi 10.1007/s10029-010-0689-5].
4. Milham S Jr. Scalp defects in infants of mothers treated for hyperthyroidism with methimazole or carbimazole during pregnancy. *Teratology* 1985; **32**:321.
5. Foulds N, Walpole I, Elmslie F, Mansour S. Carbimazole embryopathy: an emerging phenotype. *Am J Med Genet* 2005; **132A**:130–5.
6. Kannan L, Mishra S, Agarwal R, Kartikeyan V, Gupta N, Kabra M. Carbimazole embryopathy – bilateral choanal atresia and patent vitello-intestinal duct: a case report and review of literature. *Birth Defects Res A Clin Mol Teratol* 2008; **82**:649–51.
7. Wilson LC, Kerr BA, Wilkinson R, Fossard C, Donnai D. Choanal atresia and hypothelia following methimazole exposure in utero: a second report. *Am J Med Genet* 1998; **75**:220–2.
8. Clementi M, Di Gianantonio E, Pelo E, Mammi I, Basile RT, Tenconi R. Methimazole embryopathy: delineation of the phenotype. *Am J Med Genet* 1999; **83**:43–6.
9. Ferraris S, Valenzise M, Lerone M, Divizia MT, Rosaia L, Blaid D, *et al*. Malformations following methimazole exposure in utero: an open issue. *Birth Defects Res A Clin Mol Teratol* 2003; **67**:989–92.
10. Greenberg F. Choanal atresia and athelia: methimazole teratogenicity or a new syndrome? *Am J Med Genet* 1987; **28**:931–4.
11. Wolf D, Foulds N, Daya H. Antenatal carbimazole and choanal atresia. A new embryopathy. *Arch Otolaryngol Head Neck Surg* 2006; **132**:1009–11.
12. Myers AK, Reardon W. Choanal atresia – a recurrent feature of foetal carbimazole syndrome. *Clin Otolaryngol* 2005; **30**:364–83.
13. Hall BD. Methimazole as a teratogenic aetiology of choanal atresia / multiple congenital anomaly syndrome. *Am J Hum Genet* 1997; **61**:A100.
14. Barwell J, Fox G, Round J, Berg J. Choanal atresia: the result of maternal thyrotoxicosis or fetal carbimazole? *Am J Med Genet* 2002; **111**:55–6.
15. Rosenfeld H, Omoy A, Schechtman S, Diav-Citrin O. Pregnancy outcome, thyroid dysfunction, and fetal goitre after in utero exposure to propylthiouracil: a controlled cohort study. *Br J Clin Pharm* 2009; **68**:609–17.
16. Wing DA, Millar LK, Koonings PP, Montoro MN, Mestman JH. A comparison of propylthiouracil versus methimazole in the treatment of hyperthyroidism in pregnancy. *Am J Obstet Gynaecol* 1994; **170**:90–5.
17. Karlsson FA, Axelsson O, Melhus H. Severe embryopathy and exposure to methimazole in early preganancy. *J Clin Endocrinol Metab* 2002; **87**:947–8.
18. Clementi M, Di Gianantonio, Cassina M, Leoncini E, Botto L, Mastroiacovo P; SAFE-Med study group. Treatment of Hyperthyroidism in pregnancy and birth defects. *J Clin Endocrinol Metab* 2010; **95**:E337–E341.
19. Barbero P, Valdez R, Rodriguez H, Tiscornia C, Mansilla E, Allons A, *et al.* Choanal atresia associated with maternal hyperthyroidism treated with methimazole: a case-control study. *Am J Med Genet A* 2008; **146A**:2390–5.
20. Seoud M, Nassar A, Usta I, Mansour M, Salti I, Younes K. Gastrointestinal malformations in two infants born to women with hyperthyroidism untreated in the first trimester. *Am J Perinatol* 2003; **20**:59–62.
21. Abalovich M, Amino N, Barbour LA, Cobin RH, De Groot LJ, Gilinoer D, *et al.* Management of thyroid dysfunction

during pregnancy and postpartum: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2007; **92(Suppl. 8)**:S1–47.

22. Cooper DS, Rivkees SA. Putting propylthiouracil in perspective. *J Clin Endocrinol Metab* 2009; **94**:1881–2.

23. US Food and Drug Administration. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm162701.htm (Accessed 1st November 2010).