Meclizine in pregnancy in relation to congenital malformations

The suspicion that meclizine hydrochloride, an antinauseant, might cause birth defects, particularly clefts, was first raised in 1962.[1] Since then, the drug has been reported to be teratogenic in animals,[2] and conflicting reports have been published concerning its possible human teratogenicity.[2 3]

Methods and results

A total of 50 282 mother-child pairs were prospectively studied in 12 hospitals in the USA.[4] Meclizine was taken by 1014 women during the first four lunar months of pregnancy. A total of 3248 children (6·5%) were malformed. Of these, 1128 had one or more of six malformations showing considerable variability among the 12 hospitals (non-uniform malformations). Rates were reasonably uniform for all other malformations, affecting 2277 children (uniform malformations). The uniform malformations, and a subset of major malformations (1393 children), were separately evaluated, as were ten further subsets, eight of which were based on anatomical location; two further subsets comprised syndromes and tumours. Many malformed children had multiple lesions, and the subsets were not mutually exclusive. Of the non-uniform malformations, only inguinal hernia (683) and clubfoot (192) are considered here.

Various risk factors (such as parity, diabetes, cigarettes) were identified for each of the malformation outcomes.[4] For any drug exposure group, use of multiple logistic risk function models made it possible to obtain an estimate of the expected number of malformed children, in the absence of drug exposure. The ratio of the observed to the expected number gave a standardised relative risk (SRR) that simultaneously took into account potential confounding from all identified risk factors.

Malformation rates among 1014 children exposed and 49 268 non-exposed were similar for the largest outcomes (see table). Among the smaller outcomes, an association was present for defects of the eye and ear (121 children; standardised relative risk, 2·79; $P < 0.05$). None of the specific ocular defects (see foot of the table) individually accounted for the association. Four of the defects (cataract, glaucoma/buphthalmos, corneal opacity, and coloboma) were judged on embryological grounds to be of the type that could arise at any time during pregnancy[4]; there were no further cases of any of these defects among 449 additional children first exposed to meclizine after the fourth lunar month. A total of 189 children had oral clefts, of whom four had been exposed to meclizine, giving rates in the exposed and the non-exposed of 3·9 and 3·8 per 1000, respectively.

Categories of congenital malformations according to meclizine exposure during early pregnancy (lunar months 1–4)

	Exposed (1014)		Not exposed (49 268)		Standardised relative risk*	95% Confidence limits
	No	Rate/1000	No	Rate/1000		
Uniform malformations	50	49·3	2227	45·2	1·13	0·88–1·46
Major	36	35·5	1357	27·5	1·20	0·90–1·61
Central nervous	6	5·9	260	5·3	1.30	0·48–2·82
Cardiovascular	8	7·9	396	8·0	1·11	0·48–2·19
Musculoskeletal[1]	9	8·9	386	7·8	0·81	0·37–1·54
Respiratory	7	6·9	211	4·3	1·64	0·66–3·37
Gastrointestinal[2]	9	8·9	292	5·9	1·25	0·57–2·36
Genitourinary	4	3·9	180	3·7	0·92	0·25–2·35
Hypospadias[3]	4	8·4	183	7·3	1·42	0·39–3·60
Eye and ear	7[5]	6·9	114	2·3	2·79	1·12–5·73
Syndromes[4]	3	3·0	112	2·3	1·26	0·26–3·68
Tumors	2	2·0	162	3·3	0·47	0·06–1·69
Non-uniform malformations						
Inguinal hernia	18	17·8	665	13·5	1·59	0·95–2·50
Clubfoot	5	4·9	187	3·8	0·97	0·32–2·27

*Estimated by multiple logistic risk function analysis.
[1] Excludes polydactyly in black children and clubfoot.
[2] Excludes inguinal hernia.
[3] 479 male fetuses exposed, 25 063 not exposed.
[4] Excludes Down syndrome.
[5] Cataract (2); cataract, microphthalmia, glaucoma/buphthalmos (1); corneal opacity (1); glaucoma (1); coloboma (1); eye herniation, corneal opacity (1).

Discussion

Our data give no evidence that meclizine increases the overall risk of malformations; however, our confidence limits do not rule out the possibility of modest teratogenic effects. While there is no evidence of overall teratogenicity, this study raises the possibility that meclizine exposure may be related to ocular malformations. This hypothesis must be interpreted with extreme caution: although a statistically significant association was present, closer analysis did not show a relationship between meclizine and any specific eye deformity, including those that may arise in the later phases of pregnancy. Also, in this study we carried out many thousands of comparisons, from which "significant" associations were bound to arise.[4] There are no other clinical, epidemiological, or experimental data to suggest that meclizine causes ocular deformities; but eye defects in animals, resulting from cyclizine, a related compound, have been reported.[5]

There was no evidence of an association between meclizine and oral clefts, and our results accord with those of one other study.[3] Much of the suspicion that meclizine causes clefts is based on findings in animal studies, and the difficulties of generalising from such experiments to human beings are well known.

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