Is metronidazole teratogenic? A meta-analysis

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Aim In order to assess whether the use of metronidazole during pregnancy is associated with a higher risk of congenital malformations, a meta-analysis was conducted.

Methods All epidemiological studies (cohort and case-control) which estimate risk of congenital malformations after exposure to metronidazole during early pregnancy were included in the meta-analysis. To obtain a summary odds ratio, the Mantel-Haenszel method was used. A test to verify absence of heterogeneity was also performed.

Results One unpublished case-control and four published cohort studies fulfilled the inclusion criteria and were not statistically heterogeneous. A summary odds ratio was calculated for metronidazole exposure during the first trimester: OR = 1.08, 95% CI: 0.90–1.29, heterogeneity test $\chi^2 = 4.72$, $P = 0.32$.

Conclusions This meta-analysis did not find any relationship between metronidazole exposure during the first trimester of pregnancy and birth defects.

Keywords: metronidazole, malformations, meta-analysis

Introduction

Metronidazole is an antibacterial and antiprotozoal agent used in *Trichomonas* infections, amoebiasis, giardiasis, bacterial vaginosis and anaerobic infections [1]. The drug is mutagenic in bacteria and carcinogenic in rodents. It crosses the placenta to the foetus and its use in pregnancy is controversial [2]. Metronidazole is classified, according to the Food and Drug Administration (FDA) risk categories for drug use during pregnancy, as a B Risk Factor [3]: i.e. either animal reproduction studies have not demonstrated a foetal risk but there are no controlled studies in pregnant women, or animal reproduction studies have shown an adverse effect on the foetus that was not confirmed in controlled studies on women in the first trimester of pregnancy. The manufacturer and the Centers for Disease Control state that metronidazole should not be used during the first trimester. However, since no other therapy has been shown to produce an adequate response in the treatment of trichomoniasis, metronidazole can be used in pregnant women to treat such an infection during the second or third trimester [4].

Several epidemiological studies have found no risk of congenital malformations when using metronidazole during pregnancy [5–7], although another [8] found a twofold risk. In contrast, some case reports of foetal malformations have been described when the drug was used early in pregnancy [9–13].Our centre has received a report concerning the case of a new-born child with suprarenal neuroblastoma whose mother had been taking oral and intravaginal metronidazole during the first trimester of pregnancy [14].

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The wide use of metronidazole in the treatment of trichomonal or bacterial vaginosis, together with inconclusive data from the literature and the above mentioned report, led us to conduct a meta-analysis in order to clarify the safety of metronidazole use during the first trimester of pregnancy.

Methods

Study identification

A computerised Medline search combining the keywords 'metronidazole', 'pregnancy', 'teratogenic' and 'malformation' was performed from January 1966 to December 1996. Another search was carried out in the Iowa Drug Information Service (IDIS) from January 1985 to December 1996 for the drug metronidazole and the descriptor 'side effect foetal effect'. A fully recursive search of reference lists of all reviewed articles and of retrieved primary studies was also performed to find references not identified in the computerised searches. An inquiry was made at the Spanish Collaborative Study of Congenital Malformations (ECEMC, Estudio Colaborativo Español de Malformaciones Congénitas), a member of the European Network of Teratology Information (ENTIS) [15], about data available in Spain on metronidazole exposure in pregnant women and foetal malformations.

Study selection

The inclusion criteria were observational epidemiological studies, whether cohort or case-control, assessing risk of any foetal malformation associated with metronidazole use

whatever its indication during the first trimester of pregnancy. The epidemiological studies provided a group of women exposed to metronidazole during early pregnancy and another non-exposed group, with the numbers of malformations found in both groups.

Statistical analysis

This meta-analysis was conducted using the Mantel-Haenszel method [16] in order to combine information of multiple 2×2 tables. We calculated an odds ratio for each study and a summary odds ratio for all the studies, with 95% confidence intervals. The Breslow-Day test [17] was performed to verify absence of heterogeneity among the studies included in the meta-analysis.

Results

Of all the references dealing with risk of congenital malformations associated with metronidazole use during pregnancy from 1966 to 1996, only four fulfilled the inclusion criteria [5–8]. Table 1 shows the five epidemiological studies included in the meta-analysis: four published cohort studies that compared foetal malformations in pregnant women, exposed and unexposed to metronidazole, and one unpublished case-control study which also fulfilled the inclusion criteria. Risk ratios in these studies were variable and only one of them found a twofold risk, although this was not statistically significant [8].

Unpublished data collected by the ECEMC, concerning 1 113 796 live-births between April 1976 and December 1993, were also included. The design of the ECEMC is that of a case-control study including 21 078 new-borns with malformations identified within the first three days of life and 20 784 healthy new-borns in the control group. A control is defined as the next new-born to a malformed child, with the same sex and born in the same hospital. Maternal drug use was assessed by the attendant doctor during an interview with the mothers carried out within the first 3 days of delivery [18, 19]. The odds ratio calculated was 1.48 (95% confidence interval, 0.78–2.79) for exposure to metronidazole during the first trimester.

In several studies [11–13, 20–23] birth defects associated with metronidazole exposure during pregnancy were described; since all of them were case-series lacking a control group, they were excluded from the meta-analysis (Table 2).

Table 3 shows the studies included in the meta-analysis with the newly calculated individual odds ratio and their confidence intervals. The heterogeneity test was not significant, allowing these studies to be pooled, the summary odds ratio being 1.08 (95%CI: 0.90–1.29). When excluding the case-control study, the results did not differ from those obtained previously (summary odds ratio = 1.05; 95%CI: 0.87–1.27; heterogeneity test: $\chi^2 = 3.74$, $P = 0.29$).

Discussion

There are several ways in which a clinician can obtain information about drug safety during pregnancy [24]; firstly, from individual case reports and case series in the published literature, or from those coming from adverse drug reaction monitoring systems. There are some case reports of holotelencephaly, clefts in the hard and soft palate and optic atrophy in infants whose mother had been taking metronidazole in the first trimester of pregnancy [9, 10]. Some case series have also collected different malformations. In two of them, including 151 and 55 pregnant women exposed to metronidazole during the first trimester, three and four infants born with malformations, respectively, were identified [11, 12]. In another series, comprising 23 similarly exposed pregnant women [13], three pregnancies ended in spontaneous abortion and five were associated with congenital abnormalities: two with hydrocoele, one with congenital dislocation of the hip (in a female twin), another with unilateral metatarsus varus and the other with mental retardation (both parents being mentally retarded). Nevertheless, no specific malformation appeared in the different cases and, although they can warn us about the possibility of a causal relationship, this cannot be established on these premises.

Secondly, epidemiological studies constitute a better approach to the problem, but samples are often too small to acquire enough statistical power. One out of all the studies included in the meta-analysis had an odds ratio below 1, the rest having a higher value, but no risk can be established from this data since all of them included 1 in their confidence interval.

The meta-analytical method provides a quantitative approach in order to establish a more reliable estimate of the risk of metronidazole use in pregnant women. In this meta-analysis, data from a sample of more than 200 000 individuals could be pooled; and no relationship was found between birth defects and metronidazole exposure during the first trimester of pregnancy.

The studies included in this meta-analysis were all cohort or case-control in design, but there are some differences between them that should be emphasised: All the control groups consisted of healthy women except one study [5] in which the reference group was made up of pregnant women with non-treated trichomoniasis. In fact the present meta-

Table 1 Studies assessing risk of birth defects associated with metronidazole exposure during the first trimester of pregnancy included in the meta-analysis.

Study	*Year*	*Design*	n	*Malformations*
Heinonen *et al.* [8]	1977	Cohort prospective	50 282	Major
Morgan [5]	1979	Cohort prospective	350	Any
Rosa *et al.* [6]	1987	Cohort retrospective	104 339	Any
Piper *et al.* [7]	1993	Cohort retrospective	2 618	Major
ECEMC*	1994	Case-control	41 862	Any

n = number of pregnant women included in each study. *Spanish Collaborative Study of Congenital Malformations [15].

Table 2 Studies excluded from meta-analysis.

Study	*Year*	*Birth defects*	n	*Association*[a]
Scott-Gray [20]	1964	0	79	No
Robinson & Mirchandani [21]	1965	0	14	No
Rodin & Hass [22]	1966	0	13	No
Sands *et al.* [23]	1966	0	4[b]	No
Peterson *et al.* [12]	1966	4	55	Yes
Beard *et al.* [13]	1979	5	23	No
Aselton *et al.* [11]	1985	3	151	No

n = number of women exposed to metronidazole during the first trimester. [a]Association according to the author's criteria. [b]Figure obtained from graphical data.

Table 3 Studies included in the meta-analysis and odds ratio of malformations associated with metronidazole exposure during the first trimester.

	Cases of malformations[a]			
Study	*Exposed*	*Non-exposed*	*Odds Ratio*	*95% CI*
Heinonen *et al.* 1977 [8]	4/31	3244/50251	2.15	0.75–6.13
Morgan 1979 [5]	2/63	8/287	1.14	0.23–5.52
Rosa *et al.* 1987 [6]	63/1083	6501/103256	0.92	0.71–1.19
Piper *et al.* 1993 [7]	96/1307	80/1311	1.22	0.90–1.66
ECEMC (1994)	24/40	21054/41822	1.48	0.78–2.79
Summary Odds Ratio			1.08	0.90–1.29

Heterogeneity test: $\chi^2 = 4.72$, $p = 0.32$. CI = confidence intervals. [a]Number of newborn with malformations among mothers exposed or non-exposed to metronidazole during the first trimester of pregnancy.

analysis would not be able to discriminate between risk due to metronidazole and risk due to infection. There are no reports in the literature linking malformations and bacterial vaginosis, but there are evidences that link cervico-vaginal infections with preterm labour [25].

The present meta-analysis was unable to focus on any specific malformation and thus did not establish specific risks. Two of the studies [6, 7] included in the meta-analysis are retrospective studies of large computerised databases and we must note the limitations of these types of studies. Epidemiological studies based on large computerised databases are powerful tools to study associations between drugs and malformations, but the quality of the information needs to be carefully assessed. Some birth defects may not be included because they appear later after birth, and other important data are not collected, such as stillbirths or abortion. In one of the studies included in the meta-analysis [6], there was an association between spontaneous abortion and women exposed to metronidazole (RR = 1.67; 95%CI: 1.4–2.0).

Another limitation of these databases is that the exposure is based on prescriptions. It is not possible to know whether the drug is used, or not, by the patient, which dose is used, the degree of compliance, or the possible use of metronidazole from sources other than drug prescription. For this reason, doses of metronidazole are not mentioned in the present meta-analysis since the dose was only known in one of the selected studies [5].

Recently, a meta-analysis focusing on the same subject has been published [26]. That meta-analysis comprised a sample of 155 499 individuals and included, among others, 4 studies without control groups (0.3% of the total sample). We did not consider those studies without control group, but we did include a cohort study [7] not selected in Burtin's meta-analysis, in addition to the already mentioned ECEMC data. Thus, the sample size of the present study is 201 562 individuals, almost 30% more than the aforementioned meta-analysis. Nevertheless, despite the different sample size, the results of both meta-analyses are quite consistent.

Although there are some cases in the literature of malformations which occurred in women who had been exposed to metronidazole, the present meta-analysis did not find any relationship between metronidazole use in early pregnancy and birth defects.

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