Use of Cimetidine, Omeprazole, and Ranitidine in Pregnant Women and Pregnancy Outcomes

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Evidence documenting the safety of acid-suppressing drugs in pregnancy is very limited. The authors assessed the prevalence of congenital malformations in first trimester-exposed pregnancies to cimetidine, omeprazole, and ranitidine and compared it with nonexposed pregnancies between 1991 and 1996. Two different sources were used, the United Kingdom General Practice Research Database and the Italian Friuli-Venezia Giulia Health Database. The final study cohort included 1,179 pregnancies from the United Kingdom and 1,057 from Italy. Abortions or ectopic pregnancies were not included. There were 20 stillbirths and 2,261 live-born babies in both cohorts combined, with 100 offspring identified with a malformation. The overall malformation rate was 4.4%. The relative risks for nongenetic congenital malformations associated with the use of cimetidine, omeprazole, and ranitidine were 1.2 (95% confidence interval (CI): 0.6, 2.3), 0.9 (95% CI: 0.3, 2.2), and 1.4 (95% CI: 0.8, 2.4), respectively, compared with the nonexposed. No specific grouping in the distribution of malformations was observed in any of the three exposed groups. Moreover, no relation was found between drug exposure and preterm delivery or growth retardation. These findings suggest that the use of acid-suppressing drugs during the first trimester of pregnancy is not associated with a major teratogenic risk. Am J Epidemiol 1999; 150:476–81.

Drug utilization during pregnancy is rather common: 85 percent of women use at least one drug throughout their pregnancy (1). Acid-suppressing treatment is often needed in pregnancy, when acid reflux is a common complication (2). Unfortunately, as with most drugs, evidence documenting the safety of acid-suppressing drugs during pregnancy is very limited. There are only two small series published. The first one comprises 20 pregnant women exposed to H₂-blockers and one reported offspring with Down’s syndrome (3). In the other series, seven pregnant women taking omeprazole were followed up, and no congenital malformation was observed (4). Recently, a cohort study was published that included 142 pregnant women who had received H₂-blockers during the first trimester. The authors did not find an excess risk of malformations among the offspring (5). No other published epidemiologic study was found providing data on the association between exposure to H₂-blockers or proton-pump inhibitors and the risk of malformation in offspring. The purpose of this study was to assess the prevalence of infants with congenital defects among pregnant women exposed to cimetidine, omeprazole, or ranitidine during the first trimester and to compare it with the prevalence in pregnant women not taking acid-suppressing drugs during the first trimester.

MATERIALS AND METHODS

Source population

Two different sources were used to identify the cohorts of pregnancies, one in the United Kingdom and one in Italy.

We used the General Practice Research Database that includes data on about 3 million patients in the United Kingdom. General practitioners in more than 400 practices systematically enter all their patients’ medical information into computer files. This information, previously anonymous, is sent to the Office of

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Abbreviation: CI, confidence interval.
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Acid-suppressing Drugs and Pregnancy Outcomes

National Statistics, which runs numerous quality controls on the data received and prepares files appropriate for research purposes. The computerized information includes patients' demographics, diagnoses from visits to general practitioners, diagnoses from visits to specialists and hospitalizations, results of laboratory tests, and a free text section for comments. Numerous studies have been published attesting to the validity of this database for epidemiologic research (6). Furthermore, a recent study on anticonvulsant drugs and congenital malformations with the General Practice Research Database found complete concordance for congenital anomalies between the information recorded on computer and the records received from the general practitioners (7). Prescriptions issued by the general practitioner are directly generated by the computer system, and indications for new courses of treatment are regularly recorded. All subjects in the same family can be matched with a unique family code.

The region of Friuli-Venezia Giulia in northeastern Italy provides a complete panel of health services resources and maintains complete computerized files of hospitalizations since 1985, outpatient drug prescriptions since 1991, and a birth registry database starting in 1989 for the 1.2 million inhabitants of the region (8). The outpatient prescription database keeps a record of each prescription dispensed to Friuli-Venezia Giulia residents and covered by the National Health Service. The hospital services database collects data on all admissions to the public and private hospitals of Friuli-Venezia Giulia. Pregnancies were identified by means of the hospital database. The birth registry collects extensive data (more than 50 variables) on all births occurring in the region of Friuli-Venezia Giulia. Malformations at birth are recorded in this registry. In addition, infants with a malformation who require hospitalization are recorded in the hospital database. All regional databases include a unique personal identifier that enables cross-linkage among them. In addition, one can link unequivocally a mother and her children and vice versa, as there is a direct pointer between a mother and her infants in the database.

Study cohort

In the United Kingdom, we identified women younger than 45 years with a code of pregnancy between January 1991 and October 1996 and who received a prescription for one of the three acid-suppressing drugs any time from 180 days before the first recorded date of a pregnancy code until 180 days afterward. We reviewed all computerized patient profiles blinded to the exposure status of these women. We registered dates of the last menstrual period and ascertained the outcome of the pregnancy and the date. We then linked by means of the practice and family code live-born babies to their respective mothers. In Friuli-Venezia Giulia, we identified all women younger than 45 years with a hospital delivery between January 1991 and December 1996. We linked live-born babies to their mothers. We then obtained last menstrual period dates for all the women with live-born babies from the birth registry.

After ascertainment of last menstrual period dates in both data sets, we identified all women who received a prescription for cimetidine, omeprazole, or ranitidine during the first trimester of pregnancy. This period was from 30 days before the last menstrual period date (preconception period) to 100 days after the last menstrual period. Finally, we selected a group of pregnant women among the same source population originally identified but with the condition that they were not exposed to one of the three study drugs during the first trimester. In the United Kingdom, all women not exposed during that period were selected. In Italy, a random sample of all nonexposed pregnancies were selected. Women with spontaneous or voluntary abortions and ectopic pregnancies were removed from the study cohort in both data sets, as well as women receiving more than one acid-suppressing drug during the first trimester.

Case definition

Any pregnancy loss occurring at 28 weeks of gestation or after was considered stillbirth. Termination of pregnancy due to a prenatal diagnosis of malformation was grouped together with stillbirth. A case of congenital malformation was defined as any live birth or stillbirth with a structural defect and detected either prenatally, at birth, or within the first year of life. In the United Kingdom, we reviewed all infants with anomalies identified in the computer files during the first year of life. We requested copies of original medical records and hospital discharge letters from the general practitioner only in those cases where the recorded information was not sufficient to classify the malformation. In Italy, we reviewed the original, anonymous medical records and birth certificates of all babies (except one) admitted to hospitals with discharge International Classification of Diseases, Ninth Revision, codes 740–759 during the first year of life.

Analysis

Malformation prevalence rates were calculated in each exposure group using the number of offspring as the denominator. We reported estimates of relative risk and 95 percent confidence intervals using the cohort of
nonexposed pregnant women as the reference group. We did not include in this analysis birth defects known to be genetic (chromosomal and genic syndromes). We evaluated the association between first trimester exposure and the prevalence of preterm delivery (before 37 weeks). In the Friuli-Venezia Giulia data set, we also estimated the prevalence of infants who were small for gestational age (birth weight < the third percentile for gestational age) and who had a small head circumference for gestational age (head circumference < the third percentile for gestational age) (9), as well as the prevalence of hypertension and diabetes during pregnancy. All the information was retrieved directly from the birth certificate and the mother's medical records. The use of well-known teratogenic drugs (antineoplastics, anticonvulsants, retinoids, warfarin, and tetracyclines) during the first trimester of pregnancy was examined in the data set from the United Kingdom. We did not evaluate in this analysis the effect of other factors, such as smoking or alcohol consumption, during pregnancy.

**RESULTS**

Table 1 presents the different outcomes in the exposed and nonexposed groups in both data sets. The United Kingdom cohort included 1,179 pregnancies. Two pregnant women had their pregnancies terminated because of detection of a malformed baby, and 14 pregnancies ended in stillbirth (including a twin set). The remaining 1,163 pregnancies ended in delivery of 1,190 live-born babies (among them seven neonatal deaths occurred). There were 21 twin and three triplet pregnancies. We identified 68 babies with a malformation. Five infants had genetic disorders: two of them with chromosomal defects (Down's syndrome and anomaly of chromosomes 10 and 12) and three with genic disorders (Prader-Willi and Hallerman-Streiff syndromes). In Italy, 1,057 pregnancies formed the study cohort. Three ended in stillbirth, and the remaining 1,054 ended in the delivery of 1,071 live-born babies (five neonatal deaths occurred). There were 13 twin and two triplet pregnancies. We identified 32

**TABLE 1. Distribution of maternal age, pregnancy outcome, and offspring according to first trimester exposure, United Kingdom and Italy, 1991-1996**

<table>
<thead>
<tr>
<th>Pregnant women</th>
<th>Cimetidine (no.)</th>
<th>Omeprazole (no.)</th>
<th>Ranitidine (no.)</th>
<th>Nonexposed (no.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>United Kingdom cohort</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-25 years</td>
<td>223</td>
<td>97</td>
<td>224</td>
<td>635</td>
</tr>
<tr>
<td>26-35 years</td>
<td>118 (53)</td>
<td>62 (64)</td>
<td>133 (59)</td>
<td>383 (60)</td>
</tr>
<tr>
<td>36-45 years</td>
<td>35 (16)</td>
<td>11 (11)</td>
<td>38 (17)</td>
<td>74 (12)</td>
</tr>
<tr>
<td>Offspring</td>
<td>227</td>
<td>100</td>
<td>229</td>
<td>651</td>
</tr>
<tr>
<td>Stillbirths†</td>
<td>3 (1.3)</td>
<td>0</td>
<td>2 (0.9)</td>
<td>12 (1.8)</td>
</tr>
<tr>
<td>Live births‡</td>
<td>224 (98.7)</td>
<td>100 (100)</td>
<td>227 (99.1)</td>
<td>639 (98.2)</td>
</tr>
<tr>
<td>Malformed offspring</td>
<td>9 (4)</td>
<td>5 (5)</td>
<td>17 (7.4)</td>
<td>37 (5.7)</td>
</tr>
<tr>
<td>Preterm offspring (&lt;37 weeks)</td>
<td>14 (6.2)</td>
<td>7 (7)</td>
<td>23 (10)</td>
<td>48 (7.4)</td>
</tr>
<tr>
<td>Italy cohort</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnant women</td>
<td>10</td>
<td>37</td>
<td>98</td>
<td>912</td>
</tr>
<tr>
<td>15-25 years</td>
<td>3 (30)</td>
<td>4 (11)</td>
<td>27 (28)</td>
<td>163 (18)</td>
</tr>
<tr>
<td>26-35 years</td>
<td>6 (60)</td>
<td>21 (57)</td>
<td>55 (56)</td>
<td>653 (71)</td>
</tr>
<tr>
<td>36-45 years</td>
<td>1 (10)</td>
<td>12 (32)</td>
<td>16 (16)</td>
<td>96 (11)</td>
</tr>
<tr>
<td>Offspring</td>
<td>10</td>
<td>39</td>
<td>101</td>
<td>924</td>
</tr>
<tr>
<td>Stillbirths</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3 (0.3)</td>
</tr>
<tr>
<td>Live births§</td>
<td>10 (100)</td>
<td>39 (100)</td>
<td>101 (100)</td>
<td>921 (99.7)</td>
</tr>
<tr>
<td>Malformed offspring</td>
<td>2 (20)</td>
<td>0</td>
<td>3 (3)</td>
<td>27 (2.9)</td>
</tr>
<tr>
<td>Preterm offspring (&lt;37 weeks)</td>
<td>0</td>
<td>4 (10.3)</td>
<td>6 (5.9)</td>
<td>67 (7.3)</td>
</tr>
<tr>
<td>SGA¶</td>
<td>0</td>
<td>0</td>
<td>2 (2)</td>
<td>21 (2.3)</td>
</tr>
<tr>
<td>SHCGA¶</td>
<td>2 (20)</td>
<td>3 (7.7)</td>
<td>9 (8.9)</td>
<td>78 (8.5)</td>
</tr>
</tbody>
</table>

* Numbers in parentheses, percentage.
† Including two terminations of pregnancy because of a prenatal diagnosis of malformations (nonexposed).
‡ Seven neonatal deaths occurred among them (one exposed to ranitidine, one to cimetidine, and five nonexposed).
§ Five neonatal deaths occurred, all among the nonexposed group.
¶ SGA, small for gestational age (birth weight < third percentile); SHCGA, small head circumference for gestational age (head circumference < third percentile).
babies with birth defects. Only one chromosomal anomaly was detected (monosomy 18p). We found no association between drug exposure and preterm delivery, being small for gestational age, or having a small head circumference for gestational age (results not shown). Only three women (all in the nonexposed group) had diabetes before or during pregnancy, and the offspring were normal. Twenty-five women had hypertension. Among the offspring of these women, one baby was born with an ovarian cyst (in the cimetidine group), and another baby was born with polydactyly (in the nonexposed group).

Table 2 presents the type of malformation in each exposure group and in the nonexposed cohort with the United Kingdom and the Italian data sets combined. We observed an overall malformation prevalence rate of 4.4 percent (95 percent confidence interval (CI): 3.6, 5.3). The relative risks of malformations (not including genetic defects) associated with first trimester use of cimetidine, omeprazole, and ranitidine

<table>
<thead>
<tr>
<th>TABLE 2. Distribution of malformations according to first trimester exposure, aggregating cohorts from the United Kingdom and Italy, 1991–1996</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central nervous system</td>
</tr>
<tr>
<td>Spina bifida/hydrocephaly</td>
</tr>
<tr>
<td>Frontal atrophy/retinal dystrophy</td>
</tr>
<tr>
<td>Cranioorofacial</td>
</tr>
<tr>
<td>Cleft lip with cleft palate</td>
</tr>
<tr>
<td>Cleft palate only</td>
</tr>
<tr>
<td>Asymmetric skull/plagiocephaly</td>
</tr>
<tr>
<td>Accessory auricle/preauricular fistula</td>
</tr>
<tr>
<td>Tongue tie</td>
</tr>
<tr>
<td>Eye</td>
</tr>
<tr>
<td>Aniridia</td>
</tr>
<tr>
<td>Duane's eye syndrome</td>
</tr>
<tr>
<td>Cardiac</td>
</tr>
<tr>
<td>Congenital septal defects</td>
</tr>
<tr>
<td>Malformed cardiac chambers/connect</td>
</tr>
<tr>
<td>Anomalies of cardiac valves</td>
</tr>
<tr>
<td>Musculoskeletal</td>
</tr>
<tr>
<td>Accessory fingers/polydactyly</td>
</tr>
<tr>
<td>Syndactyly</td>
</tr>
<tr>
<td>Dysplastic hip/dislocation/clicking hip</td>
</tr>
<tr>
<td>Sacral sinus</td>
</tr>
<tr>
<td>Talipes varus</td>
</tr>
<tr>
<td>Genital and urinary</td>
</tr>
<tr>
<td>Hypospadias</td>
</tr>
<tr>
<td>Testes undescended</td>
</tr>
<tr>
<td>Congenital hydrocele/inguinal hernia*</td>
</tr>
<tr>
<td>Ovarian cyst</td>
</tr>
<tr>
<td>Renal defects/hydronephrosis</td>
</tr>
<tr>
<td>Potter's syndrome (bilateral renal agenesia)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>Pyloric stenosis</td>
</tr>
<tr>
<td>Polyformation</td>
</tr>
<tr>
<td>Multiple skeletal abnormalities</td>
</tr>
<tr>
<td>Pyloric stenosis and talipes equinovarus</td>
</tr>
<tr>
<td>Cleft palate and lip and auricle anomalies</td>
</tr>
<tr>
<td>Polydactyly and undescended testicle</td>
</tr>
<tr>
<td>Genetic anomalies</td>
</tr>
<tr>
<td>Hallerman-Streiff syndrome</td>
</tr>
<tr>
<td>Prader-Willi syndrome</td>
</tr>
<tr>
<td>Down's syndrome</td>
</tr>
<tr>
<td>Monosomy 18p</td>
</tr>
<tr>
<td>Anomaly of chromosomes 10 and 12</td>
</tr>
<tr>
<td><strong>Total</strong></td>
</tr>
<tr>
<td><strong>Cimetidine (no.)</strong></td>
</tr>
<tr>
<td><strong>Omeprazole (no.)</strong></td>
</tr>
<tr>
<td><strong>Ranitidine (no.)</strong></td>
</tr>
<tr>
<td><strong>Nonexposed (no.)</strong></td>
</tr>
</tbody>
</table>

* One case also had a genetic disorder (neurofibromatosis).
were 1.2 (95 percent CI: 0.6, 2.3), 0.9 (95 percent CI: 0.3, 2.2), and 1.4 (95 percent CI: 0.8, 2.4), respectively, compared with those of nonexposed women (table 3). When adjustment was made for the mothers’ age and prematurity, the relative risk of malformation associated with cimetidine was 1.3 (95 percent CI: 0.7, 2.6); with omeprazole, 0.9 (95 percent CI: 0.4, 2.4); and with ranitidine, 1.5 (95 percent CI: 0.9, 2.6). We subgrouped the cases into minor and major malformations, and the results remained virtually the same as with all malformations grouped together.

In the United Kingdom data set, we identified 30 women who took a teratogenic drug during the first trimester of pregnancy. One woman took isotretinoin, 10 took anticonvulsant drugs, and 20 took tetracyclines (one took both a tetracycline and an anticonvulsant). Only one case of malformation (pyloric stenosis) occurred in this group (cimetidine + tetracycline).

**DISCUSSION**

We have studied two cohorts of pregnant women (one in the United Kingdom and the other in Italy) to assess the incidence of malformations following first trimester exposure to cimetidine, omeprazole, or ranitidine. We did not find a major excess risk of malformations in any of these three exposed groups compared with nonexposed women. Additional studies having a larger sample size should provide more precise estimates. However, a relative risk greater than 2.5 for all malformations can be safely excluded. In addition, we did not find any specific grouping ("pattern") in the distribution of malformations in any of the three exposed groups. Moreover, no relation was found between drug exposure and preterm delivery or growth retardation. These results are in line with previous case reports and studies that did not find the use of acid-suppressing drugs (cimetidine, omeprazole, or ranitidine) during the first trimester of pregnancy to be associated with a major teratogenic risk (3–5).

At all stages of case ascertainment and validation, the exposure status of the mother was unknown to the investigators. It is important to note that the information on drug use was recorded prospectively and independently of the outcome of pregnancy. We did not consider as cases those infants with genetic defects, either chromosomal or genic syndromes, which can hardly be attributed to drug exposure (10).

There were small differences in the prevalence of defects between the cohorts from the United Kingdom and Italy. The greater number of malformations identified in the United Kingdom was the result of an excess of defects that frequently do not require a hospital admission (such as tongue tie, asymmetric skull, clicking hip, and inguinal hernia). As mentioned in Materials and Methods, malformed babies in the United Kingdom were identified through general practitioners’ records, and there was no requirement for a hospitalization to be considered a case of congenital malformation. In Italy, however, we could identify only the malformations that were either diagnosed at birth or resulted in a hospitalization. This different case ascertainment process is responsible for the small variation in prevalence (11). However, the relative risks of congenital malformation were similar in both cohorts. The relative risk of birth defects in infants whose mothers had taken any acid-suppressing drug during the first trimester of pregnancy was 1.0 (95 percent CI: 0.6, 1.6) in the United Kingdom. The corresponding relative risk in Friuli-Venezia Giulia was 1.2 (95 percent CI: 0.4, 2.9).

In conclusion, we did not find a major increased risk of malformations in babies—live births and stillbirths—whose mothers used acid-suppressing drugs during pregnancy. These results could be added to the evidence that Teratology Information Services use to inform prescribing doctors and to counsel pregnant women. Additional studies will contribute more precise estimates of risk for individual acid-suppressing drugs.

### TABLE 3. Prevalence rate and relative risk of malformation according to first trimester exposure, aggregating cohorts from the United Kingdom and Italy, 1991–1996

<table>
<thead>
<tr>
<th>Drug</th>
<th>Prevalence rate*</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonexposed</td>
<td>3.8 (3.0, 4.9)†</td>
<td>1</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>4.6 (2.6, 8.1)</td>
<td>1.2 (0.6, 2.3)</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>3.6 (1.5, 8.1)</td>
<td>0.9 (0.3, 2.2)</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>5.5 (3.5, 8.5)</td>
<td>1.4 (0.8, 2.4)</td>
</tr>
</tbody>
</table>

* Numbers refer to percentage. Genetic malformations are not included.
† Numbers in parentheses, 95% confidence interval.

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