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The safety of proton pump inhibitors in pregnancy: a multicentre prospective controlled study

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SUMMARY

Background: Proton pump inhibitors are used to treat gastro-oesophageal reflux and peptic ulcers. Gastro-oesophageal reflux is a common condition in pregnancy. Human pregnancy experience with lansoprazole or pantoprazole is very limited. More data exist on the safety of omeprazole in pregnancy.

Aim: To assess the safety of proton pump inhibitors in pregnancy.

Methods: The rate of major anomalies was compared between pregnant women exposed to omeprazole, lanzoprazole, or pantoprazole and a control group counselled for non-teratogens. The study design is a multicentre ($n = 8$), prospective, controlled study of the European Network of Teratology Information Services.

Results: We followed up 295 pregnancies exposed to omeprazole [233 in the first trimester (T_1)], 62 to lansoprazole (55 in T_1) and 53 to pantoprazole (47 in T_1), and compared pregnancy outcome to that of 868 European Network of Teratology Information Services controls. The rate of major congenital anomalies did not differ between the exposed and control groups [omeprazole nine of 249 (3.6%), lansoprazole two of 51 (3.9%) and pantoprazole one of 48 (2.1%) vs. controls 30 of 792 = 3.8%]. No differences were found when exposure was limited to the first trimester after exclusion of genetic, cytogenetic or infectious anomalies.

Conclusions: This study suggests that proton pump inhibitors do not represent a major teratogenic risk in humans.

INTRODUCTION

Proton pump inhibitors (PPIs) are used to treat gastro-oesophageal reflux (GER) and peptic ulcers. Heartburn is estimated to occur in 30–50% of all pregnancies. The origin of GER in pregnancy is multifactorial but the suggested predominant factor is a decrease in lower oesophageal sphincter pressure from progressive rise in plasma progesterone.[1] Therapy involves dietary and lifestyle modifications and non-systemic medications as the initial choices. Treatment with H_2 receptor antagonists and omeprazole can be considered in patients with refractory symptoms. PPIs offer a useful alternative to conventional therapy in the treatment of peptic ulcers. Double or triple antimicrobial therapies, in

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Table 1. Summary of published literature on omeprazole in human pregnancy

Study	Design	Number of exposed in the first trimester, risk of anomalies
Källén[6]	Prospective cohort	295, OR 0.91 (95% CI 0.45–1.84)
Lalkin *et al.*[7]	Prospective cohort	101, RR 1.68 (95% CI 0.39–7.27)
Nielsen *et al.*[8]	Retrospective cohort	38, RR 1.55 (95% CI 0.48–5.06)
Ruigomez *et al.*[9]	Retrospective cohort	139, RR 0.9 (95% CI 0.3–2.2)
Källén[10] (extended data of)[6]	Prospective cohort	863, 0.82 (95% CI 0.50–1.34)
Nikfar *et al.*[11]	Meta-analysis (five cohort studies including)[6–9]	593, RR 1.18 (95% CI 0.72–1.94)

combination with omeprazole are effective against *Helicobacter pylori*-associated peptic ulcer disease. Omeprazole has been shown to cross the human placenta.[2] Teratology studies in rats and rabbits did not produce an increase in congenital anomalies after exposure to omeprazole. Case reports[3, 4] and a case series[5] were initially published on the use of omeprazole in human pregnancy. Several studies have recently been published on the safe use of omeprazole in human pregnancy (Table 1).[6–11] Reproductive and developmental toxicity studies of lansoprazole and pantoprazole in rats and rabbits did not show an increase in congenital anomalies.[12] Human pregnancy experience with lansoprazole is very limited[6, 8, 13] and there are no studies on the use of pantoprazole in human pregnancy. Our primary objective was to prospectively evaluate the rate of major anomalies after pregnancy exposure to omeprazole, lansoprazole, or pantoprazole compared with a control group exposed to non-teratogens. Secondary endpoints of interest were pregnancy outcome, birth weight and gestational age at delivery.

MATERIALS AND METHODS

The European Network of Teratology Information Services (ENTIS) is an organization of counselling services in regard to environmental exposures during pregnancy.[14] Our multicentre prospective controlled cohort study enrolled pregnant women who or whose physician/midwife contacted one of eight Teratology Information Services (TISes) seeking counselling in regard to gestational exposure to omeprazole, lansoprazole, or pantoprazole between the years 1992 and 2001. The eight participating centres are: the Israeli TIS (Jerusalem, Israel), Pharmakovigilanz-und Beratungszentrum für Embryonaltoxikologie (Berlin, Germany), the Dutch TIS, National Institute for Public Health and the Environment (Bilthoven, The Netherlands), Servizio di Informazione Teratologica (Padova, Italy), TelefonoRosso (Rome, Italy), Institut Européen des Genomutations (Lyon, France), Teratology Information Service (Athens, Greece) and Vaestoliitto Teratology Information (Helsinki, Finland). Each of the three exposed groups was compared with an ENTIS control group of women who had been counselled during pregnancy in regard to exposures known to be non-teratogenic from seven of the eight participating centres. In order to increase the power of our study, we tried to reach a 1:2 ratio between the omeprazole exposed and control groups.

Details of exposure were collected during pregnancy before pregnancy outcome was known, using a structured questionnaire. In addition, the following information was recorded: maternal demographics, medical and obstetric histories, exposure details (dose, duration, timing in pregnancy) and concurrent exposures. After the expected date of delivery, follow-up was conducted with the woman, her physician or midwife by a telephone interview and/or mailed questionnaire to obtain details on the pregnancy outcome, gestational age at delivery, birth weight and congenital anomalies. In most cases follow-up was performed in the neonatal period.

The primary outcome of interest was the rate of major anomalies; that is, those having a structural abnormality that has serious medical, surgical, or cosmetic consequences. In the case of multiple births, each liveborn was included in the analysis. Secondary endpoints were the rates of live birth, miscarriage, pregnancy termination, stillbirth and ectopic pregnancy, the rate of premature births ($\leq$ 37 weeks), gestational age at delivery, and birth weight. Gestational age in the

present study applies to weeks post last menstrual period.

Statistical analysis

Categorical data were compared by chi-square test or Fisher exact test. Continuous data did not follow normal distribution, and were compared using the Mann–Whitney test (for two groups). The data are expressed as ratios or percentages for categorical data. Continuous data are presented using median with interquartile range. Relative risk and power calculation were performed using Epi Info 2000 software (Epi Info, Centers for Disease Control and Prevention, Atlanta Epidemiology Program Office, Atlanta, GA, USA).

RESULTS

A total of 410 pregnancies with exposure to the PPIs (295 to omeprazole, 62 to lansoprazole and 53 to pantoprazole), were prospectively followed up by the eight participating centres (164 in Jerusalem, 123 in Berlin, 61 in Bilthoven, 29 in Padova, 13 in Rome, 10 in Lyon, eight in Athens and two in Helsinki). In 86.9% of the omeprazole, 91.7% of the lansoprazole and 92.2% of the pantoprazole exposed pregnancies the exposure was in the first trimester of pregnancy. The median daily dose was 20 mg (20–40 mg) for omeprazole, 30 mg (30–60 mg) for lansoprazole and 40 mg (40–40 mg) for pantoprazole. The median duration of treatment was 22 days (4–47 days) for omeprazole, 14 days (7–32 days) for lansoprazole and 14 days (7–23 days) for pantoprazole. The most common reported indications for the PPI treatment were: as part of double or triple therapy against *H. pylori* associated peptic ulcers, peptic ulcer disease and reflux oesophagitis.

The control group included 868 pregnancies exposed to non-teratogens from seven of the eight participating centres (313 in Berlin, 216 in Jerusalem, 199 in Rome, 88 in Bilthoven, 20 in Lyon, 18 in Helsinki and 14 in Padova).

A comparison of maternal characteristics and obstetrical history between the PPI exposed and control groups is presented in Table 2. The median age of the women in the pantoprazole group was 1 year less than in the control group. A higher proportion of women in

Table 2. A comparison of maternal characteristics and obstetrical history between the proton pump inhibitor exposed and European Network of Teratology Information Services control groups

	OPZ	LPZ	PPZ	Control	P_1, P_2, P_3 values
Median age (years) interquartile range	30 (27–35)	30 (27–37)	29 (26–34)	30 (27–34)	0.973, 0.423, **0.017**
Pregnancy order	$n = 245$	$n = 52$	$n = 50$	$n = 824$	
PO 1 (%)	83 (33.9)	16 (30.8)	15 (30.0)	316 (38.3)	**<0.001**, **<0.001**, 0.118
PO 2–4 (%)	124 (50.6)	24 (46.2)	28 (56.0)	452 (54.9)	
PO ≥5 (%)	38 (15.5)*	12 (23.1)*	7 (14.0)	56 (6.8)	
Parity	$n = 244$	$n = 52$	$n = 50$	$n = 822$	
P0 (%)	99 (40.6)	19 (36.5)	19 (38.0)	366 (44.5)	**<0.001**, **0.002**, 0.084
P1–3 (%)	121 (49.6)	27 (51.9)	27 (54.0)	434 (52.8)	
≥P4 (%)	24 (9.8)*	6 (11.5)*	4 (8.0)	22 (2.7)	
Past miscarriages	$n = 242$	$n = 51$	$n = 50$	$n = 820$	
None (%)	202 (83.5)	42 (82.4)	38 (76.0)	696 (84.9)	0.755, 0.367, 0.238
1 (%)	26 (10.7)	8 (15.7)	8 (16.0)	86 (10.5)	
≥2 (%)	14 (5.8)	1 (2.0)	4 (8.0)	38 (4.6)	
Past ETOP	$n = 241$	$n = 51$	$n = 50$	$n = 820$	
None (%)	215 (89.2)	46 (90.2)	46 (92.0)	762 (92.9)	0.070, 0.167, 0.424
1	22 (9.1)	2 (3.9)	4 (8.0)	70 (6.0)	
≥2	4 (1.7)	3 (5.9)	0 (0.0)	16 (2.0)	
Median GA at call (weeks) interquartile range	9 (6–14)	8 (6–11)	8 (7–11)	11 (7–17)	**0.011**, **<0.001**, **0.003**

PO, pregnancy order; P, parity; ETOP, elective termination of pregnancy; GA, gestational age; OPZ, omeprazole; LPZ, lansoprazole; PPZ, pantoprazole; P_1, comparison between the OPZ and control groups; P_2, comparison between the LPZ and control groups; P_3, comparison between the PPZ and control groups.

* significant ($P < 0.05$) difference in comparison with the control group.

Table 3. Pregnancy outcome in the proton pump inhibitor exposed and European Network of Teratology Information Services control groups

	OPZ	LPZ	PPZ	Control	P_1, P_2, P_3 values
Live-births	247§	50¶	48	787**	
Delivery (%)	243/296†† (82.1)*	49/62 (79.0)*	48/53 (90.6)	780/868 (89.9)	**<0.001**, **0.008**, 0.869
Miscarriage (%)	24/296†† (8.1)	6/62 (9.7)	1/53 (1.9)	58/868 (6.7)	0.408, 0.430, 0.247
ETOP (%)	26/296†† (8.8)*	7/62 (11.3)*	3/53 (5.7)	27/868 (3.1)	**<0.001**, **0.005**, 0.246
Ectopic pregnancy (%)	0/296†† (0.0)	0/62 (0.0)	0/53 (0.0)	1/868 (0.1)	1.000, 1.000, 1.000
Stillbirth (%)	3/296†† (1.0)	0/62 (0.0)	1/53 (1.9)	2/868 (0.2)	0.108, 1.000, 0.163
Major anomalies (all trimesters)† (%)	9/249 (3.6)	2/51 (3.9)	1/48 (2.1)	30/792 (3.8)	0.900, 1.000, 1.000
Major anomalies (first trimester)† (%)	8/194 (4.1)	2/44 (4.6)	1/42 (2.4)	30/792 (3.8)	0.828, 0.683, 1.000
Major anomalies (first trimester) without genetic, cytogenetic, or infectious‡ (%)	6/193 (3.1)	1/44 (2.3)	0/42 (0.0)	21/788 (2.7)	0.736, 1.000, 0.619
Median GA at delivery, weeks (interquartile range)	39 (38–41)	40 (38–41)	40 (38–41)	40 (38–41)	0.101, 0.698, 0.881
Median birthweight, g (interquartile range)	3280 (2900–3600)*	3300 (2845–3615)	3280 (3020–3680)	3340 (3030–3679)	**0.020**, 0.452, 0.908
Preterm birth (≤ 37 weeks) (%)	35/228 (15.4)	7/48 (14.6)	7/48 (14.6)	86/741 (11.6)	0.135, 0.535, 0.535

ETOP, elective termination of pregnancy; GA, gestational age; OPZ, omeprazole; LPZ, lansoprazole; PPZ, pantoprazole; P_1, comparison between the OPZ and control groups; P_2, comparison between the LPZ and control groups; P_3, comparison between the PPZ and control groups.

* Significant ($P < 0.05$) difference in comparison with the control group.

† Including elective terminations of pregnancy because of prenatal diagnosis of defects.

‡ Including elective terminations of pregnancy because of prenatal diagnosis of non-genetic/non-cytogenetic/non-infectious defects.

§ Three sets of twins, one set of triplets two live-births.

¶ One set of twins.

** Seven sets of twins.

†† One triplet pregnancy considered twice (one foetus was stillborn and the others were delivered).

Table 4. Major congenital anomalies in the proton pump inhibitor exposed group

Type of anomaly	Details of exposure	Additional exposures	Source, follow-up/comments
Glanular hypospadias (grade II)	Omeprazole, T1	None	Berlin, preterm week 26 BW 350 g, ventilated 8 weeks complications of prematurity: inguinal hernia, surgical closure of PDA, ROP (laser treatment), modest motor developmental problem
Mitochondrial complex III defect – rectal atresia, tricuspid regurgitation, dysplastic left ear*	Omeprazole, T1 60 mg/day from week 8 for 8 days	None	Berlin, died on the second day of life, resistant acidosis
Unilateral renal agenesis	Omeprazole, T1 10 mg/day from LMP for 36 days	None	Berlin
Right dysplastic helix, with atresia of ear canal, possible anomaly of middle ear with normal function of inner ear	Omeprazole, T1 From week 5 for 8 days	None	Berlin
Rhizomelic limb, chondrodysplasia punctata*	Omeprazole 20 mg/day	Mesalazine, loperamide, azathioprine	Bilthoven
Clubfoot (bilateral), hypopituitarism	Omeprazole, T1	Amoxicillin – clavulanic acid	Jerusalem, casted for 8 months, then operated on, diagnosed with hypopituitarism at 4 months treated with testosterone, thyroxine
VSD	Omeprazole, T1 from week 2 for 7 days	Amoxicillin, clarithromycin, bismuth, erythromycin	Jerusalem
Exomphalos, other multiple anomalies	Omeprazole, T1 10 mg/day throughout	None	Jerusalem, ETOP week 17
Triploidy 69,XXX*	Omeprazole, T1 40 mg/day from week 2 for 6 weeks	Amoxicillin, clarithromycin	Bilthoven, ETOP week 20
Noonan syndrome 46,XX*	Lansoprazole, T1 30 mg/day from week 0 for 6 weeks	Ketotifen, haloperidol, hydroxyzine, theophylline	Lyon
Multiple anomalies (cardiac, skeletal – short limbs)	Lansoprazole, T1 from week 4 for a week	Domperidone	Jerusalem, ETOP week 25
Congenital toxoplasmosis*	Pantoprazole, T1 40 mg/day from week 2 for 8 days	None	Berlin

* Excluded when the analysis was done without genetic/cytogenetic/infectious major anomalies.
VSD, ventricular septal defect; T1, first trimester; BW, birth weight; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity; ETOP, elective termination of pregnancy.

the omeprazole and lansoprazole exposed groups called during their fifth or higher pregnancy and a higher proportion of them had four children or more compared with the control group. The women in each of the three exposed groups called at an earlier gestational age compared with the control group. There were no significant differences between the groups in the history of miscarriages or elective terminations of pregnancy (ETOP).

A comparison of pregnancy outcome between the groups is presented in Table 3. There was a higher rate of ETOP in the omeprazole and lansoprazole exposed groups compared with the control group. Two of the ETOPs in the omeprazole, one in the lansoprazole, none in the pantoprazole and five in the control groups, were because of prenatal diagnosis of anomalies. There were no differences in the rate of major anomalies between each of the three groups compared with the controls [RR 0.95 (95% CI 0.46–1.98) for omeprazole, RR 1.04 (95% CI 0.25–4.21) for lansoprazole and RR 0.55 (95% CI 0.08–3.95) for pantoprazole]. Similarly, there were no differences when this comparison was limited to PPI-first trimester exposure only and excluding genetic, cytogenetic, or infectious anomalies [RR 1.17 (95% CI 0.48–2.85) for omeprazole and RR 0.85 (95% CI 0.12–6.20) for lansoprazole]. There were no significant differences in the median gestational age at delivery or in the rate of preterm births in the exposed groups compared with the control group. A statistically significant reduction of 60 g in the median birth-weight was found in the omeprazole exposed group compared with the control group. There were no significant differences in the rate of miscarriages, ectopic pregnancies or stillbirths between the PPIs exposed groups and the control group.

The list of congenital anomalies in the PPI group is presented in Table 4. There is no pattern of anomalies.

DISCUSSION

This multicentre prospective controlled cohort study followed-up 410 pregnancies with exposure to PPIs. Both the PPI exposed and the controls had malformation rates within the expected baseline risk for the general population. The study suggests that PPIs do not represent a major teratogenic risk in humans.

A sample size of 193 omeprazole exposed live-births (first trimester exposure) with a ratio of 1:4.1 to the control group, a power of 80%, assuming a baseline risk of 3% for major anomalies enables detection of a 2.72-fold increase in the overall rate of major anomalies (with 95% confidence interval). With similar assumptions, a sample size of 44 lansoprazole exposed livebirths (ratio of 1:17.9) enables detection of a 4.75-fold increase and 42 pantoprazole exposed livebirths (ratio of 1:18.8) enables detection of a 4.90-fold increase in the overall rate of major anomalies. Our findings are consistent with the previous studies not associating omeprazole exposure during pregnancy with a teratogenic risk in humans.[6–11] If a woman requires a PPI in pregnancy, omeprazole is the one with the largest human experience.

A higher rate of ETOP in the exposed group could be related to fear of medication effect on pregnancy outcome.

The present multicentre prospective controlled cohort study, despite its limitations (i.e. reliance on self-reported drug exposure and maternal interview as a source for outcome data, population who contacted a TIS, combining data from eight TISes with different weights in the exposed and control groups, limited power on lansoprazole and pantoprazole and limited power for specific rare defects), is a valid approach to the question of the safety of PPIs in human pregnancy. The same procedure, applied to both arms of the study, and the prospective nature of the study minimize the potential biases.

In summary, the study supports that PPIs do not represent a major teratogenic risk in humans. It was powered to find a 2.72-fold increase in the overall rate of major anomalies after exposure to omeprazole. Despite the relatively large sample size, it cannot rule out an association between specific defects and PPIs exposure. Larger studies are needed for lansoprazole and pantoprazole.

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