OBSTETRICS

Increased risk of low birthweight, infants small for gestational age, and preterm delivery for women with peptic ulcer

Yi-Hua Chen, PhD; Herng-Ching Lin, PhD; Horng-Yuan Lou, MD

OBJECTIVE: The objective of the study was to determine whether maternal peptic ulcer disease (PUD) is associated with increased risk of adverse pregnancy outcomes, using a nationwide population-based dataset.

STUDY DESIGN: We identified a total of 2120 women who gave birth from 2001 to 2003 with a diagnosis of PUD during pregnancy. Then 10,600 unaffected pregnant women were matched with cases in age and year of delivery. Multivariate logistic regression analyses were performed for estimation.

RESULTS: We found that PUD was independently associated with a 1.18-fold risk of low birthweight (95% confidence interval [CI], 1.01–1.30), a 1.20-fold risk of preterm delivery (95% CI, 1.02–1.41), and a 1.25-fold (95% CI, 1.11–1.41) higher risk of babies small for gestational age, compared with unaffected mothers, after adjusting for potential confounders. In further examining women with treated PUD, improved effects of PUD medication on the risks of adverse neonate outcomes were not identified.

CONCLUSION: We document increased risk of adverse birth outcomes for women with PUD during pregnancy.

Key words: low birthweight, peptic ulcer, pregnancy outcome, preterm birth, small for gestational age

Cite this article as: Chen Y-H, Lin H-C, Lou H-Y. Increased risk of low birthweight, infants small for gestational age, and preterm delivery for women with peptic ulcer. Am J Obstet Gynecol 2010;202:164.e1-8.

Although peptic ulcer disease (PUD) is common worldwide,[1] epidemiologic studies reveal a decrease in incidence and support an alleviation of PUD during pregnancy.[2-7] Cappell and Sidhom[8] reported that of 29,317 pregnant patients, 56 pregnant women who were hospitalized (0.19%) were found to have severe upper gastrointestinal complaints. Only 2 of 20 of the women undergoing esophagogastroduodenoscopy (EGD) were identified as having PUD (specifically for duodenal ulcers).

PUD, with its chronic and recurrent course, may complicate pregnancy.[9] However, tests to evaluate suspected PUD (eg, upper gastrointestinal series or EGD) that are routine in the general population have been conservatively performed on pregnant women.[10,11] Potential risks of concern include fetal hypoxia because of maternal hypotension and hypoxia or inferior vena caval compression by the pregnant uterus as well as exposure to potentially teratogenic drugs and radiation.[12] Although avoiding invasive tests during pregnancy, clinicians frequently have to manage and prescribe medication to treat symptoms of either PUD or gastroesophageal reflux disease of undetermined origin.

Investigation of pregnancy outcomes is thus essential for evaluating the fetal and maternal risk of clinical care for PUD and its appropriateness for pregnant women. Nevertheless, no study to date has reported on the effect of maternal PUD on fetal outcomes. Furthermore, no study has specifically distinguished the extent of fetal risk from treated and untreated maternal PUD during pregnancy.

Thus, the objective of this nationwide, population-based study was to determine whether PUD in pregnancy is associated with adverse pregnancy outcomes, specifically low birthweight (LBW), small for gestational age (SGA), and preterm delivery, as compared with pregnant women without PUD. Whether women with treated PUD possessed altered risks in terms of fetal outcomes was examined further.

Materials and Methods

Databases

This study used 2 large-scale, nationwide, population-based datasets. The first dataset was sourced from the 2000-2003 National Health Insurance Research Dataset (NHIRD), published by the National Health Research Institute in Taiwan. The NHIRD consists of registries of contracted medical facilities and board-certified physicians along with inpatient and ambulatory care claims for more than 22 million enrollees, more than 98% of the island's population. The NHIRD provides 1 principal diagnosis from the *International Classification of Disease, Ninth Revision,* Clinical Modification (ICD-9-CM) code and up to 4 secondary ICD-9-CM diagnoses for each patient.

The second database used in this study is obtained from the birth certificate registry published by Taiwan's Ministry of the Interior. The data on birth certificates include both infants' and parents' birth dates, gestational week at birth,

From the School of Public Health (Dr Chen), the School of Health Care Administration (Dr Lin), and the Division of Gastroenterology, Department of Internal Medicine (Dr Lou), Taipei Medical University Hospital, Taipei, Taiwan.

Received March 24, 2009; revised June 21, 2009; accepted Sept. 24, 2009.

Reprints: Herng-Ching Lin, PhD, School of Health Care Administration, Taipei Medical University, 250 Wu-Hsing St., Taipei 110, Taiwan. henry11111@tmu.edu.tw.

0002-9378/$36.00

doi: 10.1016/j.ajog.2009.09.029

birthweight, sex, parity, place of birth, parental educational levels, and maternal marital status. The registration of all births is mandatory in Taiwan, and the completeness and validity of Taiwan's birth registry has been verified.[13]

With assistance from the Bureau of the National Health Insurance (NHI) in Taiwan, the mother's and infant's unique personal identification numbers provided links between the NHIRD and birth certificate data. Confidentiality assurances were addressed by abiding by the data regulations of the NHI. All personal identifiers were encrypted by the NHI before release to the researchers. Because the NHIRD consists of deidentified secondary data released to the public for research purposes, this study was exempt from full review by the internal review board.

Study sample

We identified a total of 473,529 women who had singleton births in Taiwan between Jan. 1, 2001, and Dec. 31, 2003. If a mother had more than 1 singleton birth during the study period, we selected only the first for the study sample. Of these women, 23,822 were identified as having visited ambulatory care clinics or outpatient departments of hospitals for treatment of peptic ulcer (ICD-9-CM code 531-533) during pregnancy.

Because many researchers question the coding validity of administrative databases, for the study cohort, we selected patients who had at least 3 consensus peptic ulcer diagnoses during pregnancy and who had undergone EGD test to confirm their PUD diagnosis within the 2 years preceding the index pregnancy. This left a total of 2120 women with PUD for analysis.

Our comparison cohort was extracted from the remaining 449,707 mothers. We randomly selected 10,600 women (5 for every mother with peptic ulcers) matched with the study group in terms of age (<20, 20-24, 25-29, 30-34, and ≥35 years) and year of delivery.

Variables of interest

The dependent variables were all dichotomous: whether an infant had LBW, preterm gestation, or was SGA. According the World Health Organization, the standard cutoff point for LBW is 2500 g (<2500 g, ≥2500 g). Preterm birth was defined as birth occurring at a gestational age less than 37 weeks, and SGA is defined as birthweight below the 10th percentile for gestational age. Savitz et al[14] proposed a lack of concordance among these adverse fetal outcomes. Manifold outcome measures should be assessed, with the results from each measure examined separately.[14] Our study thus adopted multiple outcomes for evaluation.

The key independent variable of interest was whether a mother had visited ambulatory care centers for the treatment of PUD during their pregnancy. A further dichotomous variable was generated for the women with PUD to distinguish those who received medications such as H_2 blockers or proton pump inhibitors for more than 1 month during pregnancy and those who did not.

Other potential confounders contributing to pregnancy outcomes were also taken into consideration. These included characteristics of the infant (sex), mother (age, parity, the highest education level, and marital status), father (age and the highest education level), and family monthly income (including mothers' and fathers' monthly income). Parental age difference was also included because of its documented effects on birth outcomes, irrespective of any uniquely maternal characteristics.[15]

Statistical analysis

The SAS statistical package (SAS System for Windows, version 8.2; SAS Institute, Inc., Chicago, IL) was used to perform all analyses in this study. Pearson χ^2 tests were used to examine the differences in characteristics of mother, father, and infant comparing women with PUD and unaffected women. Multivariate logistic regression analyses were used to calculate the risk of LBW, preterm gestation, and SGA for these 2 cohorts. A significance level of .05 was selected to determine the significance of predictors in the models.

RESULTS

Table 1 describes the details of the distribution of characteristics of mothers and fathers, comparing women with PUD and unaffected women. Pearson χ^2 tests show that there were significant differences between the 2 cohorts in terms of mothers' parity ($P < .001$), hypertension ($P = .008$), renal disease ($P = .004$), coronary heart disease ($P = .035$), hyperlipidemia ($P < .001$), and family monthly income ($P = .010$).

Infant characteristics, comparing the mothers with PUD and unaffected women, are given in Table 2. The infants of mothers with PUD during pregnancy had significantly lower birthweights (3065 ± 456 vs 3113 ± 480 g; $P = .003$) and shorter gestational ages at delivery (38.2 ± 2.8 vs 38.5 ± 2.2 weeks; $P < .001$), compared with women without PUD.

Table 3 describes the distribution and crude and adjusted odds ratios of LBW, preterm birth, and SGA for the 2 cohorts. Pearson χ^2 tests show that there were significant differences between women with PUD and unaffected women in terms of LBW (8.2% vs 6.9%; $P = .029$), preterm birth (9.7% vs 8.1%; $P = .015$), and SGA (20.9% vs 17.0%; $P < .001$).

The regression analyses also show that women with PUD were more likely to have LBW infants (odds ratio [OR], 1.21; 95% confidence interval [CI], 1.02–1.44), preterm births (OR, 1.22; 95% CI, 1.04–1.43), and SGA babies (OR, 1.28; 95% CI, 1.14–1.44) than unaffected mothers.

Next, multivariate logistic regression models were performed. Because of the identification of a strong collinearity between maternal and paternal age, we kept only maternal age and added age differences between parents in the models. Thus, after adjusting for the infant's sex, maternal age, parity, highest maternal and paternal educational level (separately), parental age difference, mothers' marital status, gestational hypertension, diabetes, renal disease, coronary heart disease, hyperlipidemia, and family monthly income, the odds of LBW, preterm birth, and SGA for women with PUD during pregnancy were 1.18 times (95% CI, 1.01–1.30), 1.20 (95% CI, 1.02–1.41), and 1.25 (95% CI, 1.11–1.41) that of unaffected women.

To separate the effects of medication taken for this disorder during pregnancy

TABLE 1
Comparison of maternal and paternal characteristics among pregnant women with peptic ulcers and unaffected mothers in Taiwan, 2001-2003 (n = 12,720)

	Mothers with peptic ulcers (n = 2120)		Comparison mothers (n = 10,600)		
Variable	**Total**	**%**	**Total**	**%**	***P* value**
Maternal characteristics					
Age, y					1.000
<20	87	4.1	435	4.1	
20-24	418	19.7	2090	19.7	
25-29	724	34.2	3620	34.2	
30-34	590	27.8	2950	27.8	
>34	301	14.2	1505	14.2	
Parity					< .001
1	1167	55.0	5445	51.4	
2	612	28.9	3540	33.4	
≥3	341	16.1	1615	15.2	
Education level					.659
Elementary school or lower	51	2.4	221	2.1	
Junior high school	340	16.0	1748	16.5	
Senior high school	1429	67.4	7070	66.7	
College or above	300	14.2	1561	14.7	
Marital status					.760
Married	2050	96.7	10,236	96.6	
Others	70	3.3	364	3.4	
Gestational diabetes					.401
Yes	183	8.6	857	8.1	
No	1937	91.4	9743	91.9	
Hypertension					.008
Yes	52	2.5	172	1.6	
No	2068	97.5	10,428	98.4	
Renal disease					.004
Yes	7	0.33	9	0.1	
No	2113	99.7	10,591	99.9	
Coronary heart disease					.035
Yes	30	1.4	97	0.9	
No	2090	98.6	10,503	99.1	
Hyperlipidemia					< .001
Yes	44	2.1	122	1.2	
No	2076	97.9	10,478	98.8	

Chen. Pregnancy outcome for women with peptic ulcer. Am J Obstet Gynecol 2010. *(continued)*

TABLE 1
Comparison of maternal and paternal characteristics among pregnant women with peptic ulcers and unaffected mothers in Taiwan, 2001-2003 (n = 12,720) *(continued)*

	Mothers with peptic ulcers (n = 2120)		Comparison mothers (n = 10,600)		
Variable	**Total**	**%**	**Total**	**%**	***P* value**
Family monthly income					.010
NT <$15,000	783	36.9	3730	35.2	
NT $15,000-30,000	529	25.0	2609	24.6	
NT $30,001-50,000	569	26.8	2779	26.2	
NT >$50,000	239	11.3	1482	14.0	
Paternal characteristics					
Age, y					.619
<30	782	36.9	3972	37.5	
30-34	739	34.9	3743	35.3	
>34	599	28.2	2885	27.2	
Education level					.227
Elementary school or lower	41	1.9	161	1.5	
Junior high school	384	18.1	1996	18.8	
Senior high school	1325	62.5	6469	61.0	
College or above	370	17.5	1974	18.6	

NT, New Taiwan.

Chen. Pregnancy outcome for women with peptic ulcer. Am J Obstet Gynecol 2010.

on pregnancy outcomes, we divided women with peptic ulcers into 2 groups: those who had received medications such as H_2 blockers or proton pump inhibitors for the treatment of peptic ulcers for more than 1 month of pregnancy and those who had not.

We found that after adjusting for potential confounders, women who had received no medication for the treatment of PUD during pregnancy still had higher odds of LBW (OR, 1.18; 95% CI, 1.01–1.41), preterm birth (OR, 1.18; 95% CI, 1.01–1.40), and SGA (OR, 1.29; 95% CI, 1.14–1.46) than unaffected women (Table 4). This implies that the PUD was an independent risk factor for LBW, preterm birth, and SGA.

Comment

This is the first report of pregnancy outcomes among women with PUD during gestation. Our nationwide, population-based study revealed that maternal PUD was independently associated with a 1.18-, 1.20-, and 1.25-fold increased risk of having babies with LBW, preterm delivery, and SGA,

TABLE 2
Comparison of infant characteristics among pregnant women with peptic ulcers and unaffected mothers in Taiwan, 2001-2003 (n = 12,720)

	Mothers with peptic ulcers (n = 2120)			Comparison mothers (n = 10,600)			
Variable	**Total**	**%**	**Mean (SD)**	**Total**	**%**	**Mean (SD)**	***P* value**
Infant characteristics							
Gender							.043
Male	1096	51.7		5734	54.1		
Female	1024	48.3		4866	45.9		
Birthweight, g			3065 (456)			3113 (480)	.003
Gestational age at delivery, wks			38.2 (2.8)			38.5 (2.2)	< .001

Chen. Pregnancy outcome for women with peptic ulcer. Am J Obstet Gynecol 2010.

TABLE 3
Crude and adjusted ORs of LBW, preterm, and SGA babies between mothers with peptic ulcers and unaffected mothers, 2001-2003 (n = 12,720)

	Mothers with peptic ulcers (n = 2120)		Comparison mothers (n = 10,600)		
Variable	**Total**	**%**	**Total**	**%**	***P* value**
Low birthweight					.029
Yes	174	8.2	729	6.9	
No	1946	91.8	9871	93.1	
Crude OR (95% CI)	1.21 (1.02–1.44)[b]		1.00		
Adjusted OR (95% CI)[a]	1.18 (1.01–1.30)[b]		1.00		
Preterm birth					.015
Yes	206	9.7	860	8.1	
No	1914	90.3	9740	91.9	
Crude OR (95% CI)	1.22 (1.04–1.43)[b]		1.00		
Adjusted OR (95% CI)[a]	1.20 (1.02–1.41)[c]		1.00		
Small for gestational age					< .001
Yes	442	20.9	1805	17.0	
No	1678	79.1	8795	83.0	
Crude OR (95% CI)	1.28 (1.14–1.44)[c]		1.00		
Adjusted OR (95% CI)[a]	1.25 (1.11–1.41)[c]		1.00		

CI, confidence interval; *OR*, odds ratio.

[a] Adjusted for infant's sex, maternal age, parity, highest maternal educational level, parental age difference, mothers' marital status, and family monthly income as well as gestational hypertension, diabetes, hyperlipidemia, renal disease, and coronary heart disease; [b] $P < .05$; [c] $P < .001$.

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respectively, after adjusting for family income and maternal, paternal, and infant characteristics.

We further evaluated the effects of PUD medication during pregnancy. With the comparison of the PUD women without treatment with the unaffected mothers, gestational PUD was found to have an adverse impact on pregnancy outcomes. However, in further examining women with treated PUD, we were unable to identify improved effects of PUD medication on the risks of adverse neonate outcomes.

Some previous studies have reported increased risk of adverse pregnancy outcomes among women with gastrointestinal diseases. For example, a metaanalysis of 12 studies examining 3907 patients identified 1.5- and 1.87-fold increased risks of caesarean delivery and preterm birth, respectively, among women with inflammatory bowel disease compared with controls. The incidence of LBW doubled.[16]

No increased risk of adverse pregnancy outcomes was identified among women with inactive inflammatory bowel disease. However, increased risk of LBW and preterm birth was observed among mothers diagnosed with Crohn's disease, especially those who were active cases.[17] Studies of other gastrointestinal diseases that are incidental to pregnancy (eg, dyspepsia) but not specific to gestation (eg, obstetric cholestasis and HELLP [hemolysis, elevated liver enzymes, and low platelet count] syndrome) are scant.

Our results are unique in demonstrating increased risk of adverse birth outcomes, specifically LBW, preterm birth, and SGA, among mothers with PUD, compared with unaffected women.

It is also worth noting that increased rates of hypertension, hyperlipidemia, coronary heart disease, and renal disease were observed for women with PUD compared with unaffected mothers. Previous studies have reported high comorbidity of PUD with chronic diseases including liver cirrhosis, rheumatoid arthritis, and ischemic heart disease.[18,19] A shared common etiologic factor was proposed to explain the strong association,[19] and further studies are needed to clarify specific relationships.

It remains unclear what factors elevate the risk of adverse birth outcomes among patients with PUD. The possible role of diet and nutrient absorption deserve more examination. In animal models, maternal starvation decreased the extent of metabolic substrate produced by the mother and provided to the fetus, retarding fetal intrauterine growth.[20] Glucose, transmitted from mother to fetus, is the main energy substrate for intrauterine growth.[21] Whereas glucose is produced by maternal metabolism, dietary restriction or maternal hypoglycemia decrease availability of metabolic fuel and consequently slow fetal growth.[22,23] Likewise, low micronutrient intake during pregnancy is associated with adverse neonatal outcomes such as preterm delivery.[20]

TABLE 4
Crude and adjusted OR for LBW, preterm birth, and SGA babies between mothers with peptic ulcers and unaffected mothers, 2001-2003 (n = 12,720)

			Mothers with peptic ulcers			
	Comparison mothers (n = 10,600)		Women not prescribed medication for peptic ulcers during pregnancy (n = 1898)		Women prescribed medication including H_2 blockers or proton pump inhibitors for treatment of peptic ulcers during pregnancy (n = 222)	
Variable	Total	%	Total	%	Total	%
Low birthweight						
Yes	729	6.9	156	8.2	18	8.1
No	9871	93.1	1742	91.8	204	91.9
Crude OR (95% CI)	1.00		1.21 (1.01–1.45)[b]		1.20 (0.73–1.95)	
Adjusted OR (95% CI)[a]	1.00		1.18 (1.01–1.41)[b]		1.18 (0.72–1.92)	
Preterm birth						
Yes	860	8.1	182	9.6	24	10.8
No	9740	91.9	1716	90.4	198	89.2
Crude OR (95% CI)	1.00		1.20 (1.02–1.42)[b]		1.37 (0.89–2.11)	
Adjusted OR (95% CI)[a]	1.00		1.18 (1.01–1.40)[b]		1.39 (0.90–2.14)	
Small for gestational age						
Yes	1805	17.0	405	21.3	37	16.7
No	8795	83.0	1493	78.7	185	83.3
Crude OR (95% CI)	1.00		1.32 (1.17–1.49)[c]		0.98 (0.68–1.39)	
Adjusted OR (95% CI)[a]	1.00		1.29 (1.14–1.46)[c]		0.95 (0.67–1.36)	

CI, confidence interval; *OR*, odds ratio.

[a] Adjusted for infant's sex, maternal age, parity, highest maternal and paternal education level (separately), parental age difference, mothers' marital status, and family monthly income as well as gestational hypertension, diabetes, hyperlipidemia, renal disease, and coronary heart disease; [b] $P < .05$; [c] $P < .001$.

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In response to symptoms of anorexia, abdominal distention, epigastric pain, and postprandial vomiting, mothers with PUD during pregnancy may restrict their dietary intake to avoid the discomfort. The risk of constrained fetal growth and adverse birth outcomes might be elevated accordingly.

Stress might also contribute to the link between gestational PUD and adverse pregnancy outcomes. Stress is strongly associated with PUD because threats to homeostasis prompt an adaptive or allostatic response.[24] Maternal vasoconstriction, resulting from the release of catecholamines in exposure to stress, might also obstruct the transmission of oxygen and vital nutrients to the fetus.[25] Fetal central nervous system and particularly glucocorticoid brain receptor development might subsequently be affected.[26,27]

Previous literature indeed demonstrated a significant relationship between maternal prenatal stress and infants with low birthweights and decreased gestational age at birth.[27] Thus, women with PUD might be those who perceive or experience more stressful circumstances. The further exposure of their fetuses to stress and elevated levels of adrenal hormones might consequently elevate the risk of negative birth outcomes.

Furthermore, we identified increased risk of adverse pregnancy outcomes among mothers with PUD who took no medication for it during pregnancy. Meanwhile, no significant difference in outcomes was observed for those who did take medication during pregnancy. PUD medication, such as H_2 blockers or proton pump inhibitors,[28-30] is probably safe during pregnancy according to current clinical data.

We should consider the possibility that the lack of insignificant difference was due to the relatively small sample size, resulting in insufficient statistical power, for this group. The trend toward slightly increased though insignificant risk of LBW and preterm birth might reflect more severe PUD symptoms among women who were prescribed PUD medication.

Our study breaks new ground by examining adverse pregnancy outcomes among women with PUD. The nationwide, population-based data provided by linking the NHIRD with the national birth registry leave little room for selec-

tion and nonresponse bias. Our results may be confidently generalized to the population as a whole.

Four limitations of this study merit attention. First, the NHIRD database represents only patients who sought treatment. The validity of the PUD diagnoses could also be a concern. However, our study cohort consisted of women who had at least 3 consensus PUD diagnoses during pregnancy and who had EGD tests performed to confirm PUD diagnosis in the 2 years preceding the index pregnancy. Because of PUD's chronic and recurrent course, diagnostic validity should be justified.

Second, this dataset did not allow us to consider differences in PUD severity among patients. Third, because we attempted to differentiate risk for women who did and did not take PUD medication during pregnancy, it is possible that the group of women with PUD who were not prescribed medication was not the same as the group of women who required medication during pregnancy. Also, pregnant women with PUD might discontinue prescribed medication without consulting their physicians.

Lastly, because of reliance on a claims database, our study was unable to include risk factors such as cigarette smoking, alcohol consumption, and dietary habits in the regression model, potentially compromising our findings.

There are substantial implications of this study. Because mothers with PUD during pregnancy were at higher risk for adverse birth outcomes, our results provide a compelling reason for making prevention of PUD occurring during gestation a goal of clinical practice for women with a history of PUD. Therapeutic recommendations during pregnancy may be modified to be more conservative out of concern for fetal safety.

Given its chronic and recurrent course, we suggest treating PUD before conception, when proton pump inhibitors and H_2 blockers can be prescribed early and assertively because of their high efficacy and patient safety.[31] In addition, as much as 80% of ulcers are associated with *Helicobacter pylori*.[32] Triple-drug therapy for *H pylori* infection, usually including 2 antibiotics and 1 potent acid-suppressive medication, can be more aggressively prescribed for nonpregnant women.[2] Then dietary changes as both a supportive and therapeutic method, may help manage PUD in the longer run. Better intervention to avoid PUD during pregnancy could reduce the impact of PUD on fetal outcomes.

Because of the increased risk of adverse birth outcomes among pregnant women with PUD, a multidisciplinary team approach to providing obstetric care with the goal of preventing, monitoring, and intervening in PUD is important. The association between gestational PUD and adverse fetal outcomes requires confirmation and replication in future larger studies. The mechanisms of this link also warrant further investigation.

First, we found that PUD was independently associated with a 1.18-, 1.20-, and 1.25-fold risk of infants with LBW, preterm, and SGA, compared with infants of unaffected mothers. Second, further examining the effects of treatment for PUD on neonatal outcomes, we were unable to identify improvement in risk for adverse neonatal outcomes of PUD medication. And lastly, our study documents increased risk of adverse birth outcomes for women with PUD during pregnancy. ■

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