Antiglaucoma medications during pregnancy and the risk of low birth weight: a population-based study

J-D Ho,[1,2] C-C Hu,[3,4] H-C Lin[5]

[1] Department of Ophthalmology, Taipei Medical University Hospital, Taipei, Taiwan; [2] Department of Ophthalmology, Taipei Medical University, Taipei, Taiwan; [3] Department of Ophthalmology, Shin Kong Wu-HoSu Memorial Hospital, Taipei, Taiwan; [4] School of Medicine, Fu-Jen Catholic University, Taipei, Taiwan; [5] School of Health Care Administration, Taipei Medical University, Taipei, Taiwan

Correspondence to: Professor H-C Lin, School of Health Care Administration, Taipei Medical University, 250 Wu-Hsing Street, Taipei 110, Taiwan; henry11111@tmu.edu.tw

Accepted 2 May 2009
Published Online First 10 June 2009

ABSTRACT

Objective: To study the relationship between using antiglaucoma medications during pregnancy and the risk of having low-birth-weight (LBW) infants.

Methods: The study group comprised 244 pregnant women who had been prescribed topical medication to control glaucoma during pregnancy. The comparison group comprised 1952 pregnant women matched for age, year of delivery, maternal hypertension and gestational diabetes. Multivariate logistic regressions were conducted to calculate the adjusted odds ratio of having LBW infants.

Results: The majority of pregnant women (77.5%) were prescribed beta-blockers to control glaucoma. After adjusting for characteristics of the infant (gender, parity and gestational age), mother (age, the highest educational level, marital status, hypertension and gestational diabetes), father (the highest educational level), parental age difference and family monthly income, there was no significant difference in the risk of LBW infants between mothers prescribed beta-blockers and mothers in the comparison cohort (adjusted odds ratio (OR) 1.48, 95% CI 0.86 to 2.56). However, there was a significantly higher risk of LBW infants for mothers prescribed topical antiglaucoma medications other than beta-blockers (adjusted OR 2.15, 95% CI 1.05 to 5.00).

Conclusions: Topical beta-blockers can be the first-line drugs when considering medical treatment of glaucoma in a pregnant woman.

Although intraocular pressure (IOP) in pregnant women with ocular hypertension may decrease in the second and third trimesters,[1] some pregnant women continue to have a high IOP and require treatment.[2–6] However, management of glaucoma during pregnancy is challenging. In a survey of ophthalmologists in the UK, 26% had previously treated pregnant women with glaucoma.[7] When asked what they would currently do, 31% were unsure how to treat a pregnant woman whose IOP seemed likely to cause disease progression during pregnancy; 40% would use (or continue to use) topical treatment. Of those who would prescribe medical treatment, 45% would use topical beta-blockers first, 33% would use topical prostaglandin analogues first, and 22% would use other medications first. It is not surprising that such a high proportion of ophthalmologists were unsure how to treat glaucoma in pregnant women or that their drugs of first choice differed, because current evidence is insufficient to confirm that antiglaucoma drugs are absolutely safe for pregnant women. While some antiglaucoma medications are deemed anecdotally to be safe for pregnant women, no large-scale study has been published, to the best of our knowledge. Ophthalmologists have had to rely on information gathered from case studies.[3]

Using a population-based dataset from Taiwan, this study investigates the relationship between different categories of antiglaucoma medications during pregnancy and the risk of having a low-birth-weight (LBW) infant.

METHODS

Database

Two national databases were used in this study. The first was the 1996–2003 National Health Insurance Research Dataset (NHIRD), published by the National Health Research Institute in Taiwan. Taiwan's National Health Insurance programme was implemented in 1995. The NHIRD includes inpatient and ambulatory care claims for over 22 million Taiwanese enrollees, representing over 98% of the island's population.

The second database used in this study was the birth certificate registry published by the Ministry of Interior in Taiwan. Because the registration of all births and deaths is mandatory in Taiwan, birth certificate data in Taiwan are believed to be accurate and comprehensive. With assistance from the Bureau of the National Health Insurance (NHI) in Taiwan, mothers' and infants' unique personal identification numbers provided links between the NHIRD and birth certificate data.

Study sample

We initially identified 477 006 mothers having singleton births in Taiwan between 1 January 2001 and 31 December 2003. Of these, 252 had been prescribed topical antiglaucoma medication during pregnancy. We excluded those who had been prescribed more than one category of topical ophthalmic medication (n = 8), leaving 244 mothers as a study cohort for analysis.

Our comparison cohort was extracted from the remaining 476 754 mothers. We excluded women diagnosed as having any type of mental disorder, systemic lupus erythematosus, rheumatoid arthritis, gout, sarcoidosis or ankylosing spondylitis between 1996 and 2003. We then randomly selected 1952 mothers (eight for every one in the study cohort) matched in terms of age (<25, 25–29, 30–34 and ≥35 years), the year of delivery and whether or not a woman had hypertension or gestational diabetes.

Variables of interest

In this study, the dependent variable was dichotomous—whether or not an infant had an LBW.

According the World Health Organization, the standard cut-off point for LBW in infants is 2500 g (<2500 g, ⩾2500 g). The key independent variable was whether a woman had topical ophthalmic medication prescribed to control intraocular pressure during pregnancy.

Other possible factors contributing to pregnancy outcomes were also adjusted for in this study, including characteristics of the infant (gender, parity and gestational age), mother (age, highest educational level, marital status, hypertension and gestational diabetes), father (age and the highest educational level), parental age difference and family monthly income (including mothers' and fathers' monthly income). Gestational age was used to adjust for the effect of preterm births (<37 weeks). Maternal and paternal education was categorised into four levels: elementary school or lower, junior high school, senior high school, college or above.

Table 1 Comparisons of women who used topical antiglaucoma medication during pregnancy and women with no chronic disease in relation to maternal, paternal and infant characteristics in Taiwan, 2001~2003 (χ^2 tests)

	Mothers with no history of chronic disease	Mothers who used topical antiglaucoma medication during pregnancy	
	n = 1952	n = 244	
Variable	Total no (%)	Total no (%)	p Value
Birth weight (g), mean (range)	3134 (2232)	3060 (2221)	0.032
Infant characteristics			
Gender			0.119
Male	1025 (52.5)	141 (57.8)	
Female	927 (47.5)	103 (42.2)	
Parity			0.038
1	896 (45.9)	133 (54.5)	
2	738 (37.8)	79 (32.4)	
⩾3	318 (16.3)	32 (13.1)	
Gestational age (weeks)			0.128
<37	146 (7.5)	25 (10.2)	
⩾37	1806 (92.5)	219 (89.8)	
Maternal characteristics			
Age (years)			1.000
<25	288 (14.8)	36 (14.8)	
25–29	648 (33.2)	81 (33.2)	
30–34	752 (38.5)	94 (38.5)	
>34	264 (13.5)	33 (13.5)	
Education level			0.284
Elementary school or lower	50 (2.6)	2 (0.8)	
Junior high school	283 (14.5)	31 (12.7)	
Senior high school	1295 (66.3)	166 (68.0)	
College or above	324 (16.6)	45 (18.4)	
Marital status			0.479
Married	1906 (97.6)	240 (98.4)	
Others	46 (2.4)	4 (1.6)	
Gestational hypertension			1.000
Yes	49 (2.5)	6 (2.5)	
No	1903 (97.5)	238 (97.5)	
Gestational diabetes			1.000
Yes	41 (2.1)	5 (2.1)	
No	1911 (97.9)	239 (97.9)	
Family monthly income			0.276
<NT$15 000	551 (28.2)	70 (28.7)	
NT$15 000–30 000	497 (25.5)	58 (23.8)	
NT$30 001–50 000	601 (30.8)	67 (27.5)	
>NT$50 000	303 (15.5)	49 (20.0)	
Paternal characteristics			
Age			0.885
<30	566 (29.0)	74 (30.3)	
30–34	780 (40.0)	94 (38.5)	
>34	606 (31.0)	76 (31.2)	
Education level			0.556
Elementary school or lower	33 (1.7)	3 (1.2)	
Junior high school	322 (16.5)	45 (18.4)	
Senior high school	1192 (61.1)	139 (57.0)	
College or above	405 (20.8)	57 (23.4)	

Statistical analysis

The SAS statistical package (SAS System for Windows, Version 8.2) was used to perform all analyses in this study. χ^2 tests were utilised for comparisons of the infant, maternal, paternal and family characteristics between the study and comparison cohorts. Multivariate logistic regression analyses were conducted to calculate the adjusted odds ratio of having an LBW infant for mothers prescribed different categories of topical antiglaucoma medications during pregnancy in relation to a comparison group after adjusting for characteristics of the infant (gender, parity and gestational age), mother (age, the highest educational level, marital status, hypertension and gestational diabetes), father (highest educational level), parental age difference and family monthly income. (We found a strong collinearity between maternal and paternal age, so we kept only maternal age in the regression model.) A two-sided p value of <0.05 was considered statistically significant for this study.

RESULTS

Table 1 shows a significant difference in parity ($p = 0.038$, χ^2 test) between the two cohorts; mothers in the study cohort were more likely to be primigravida than their counterparts in the comparison cohort. No significant difference was observed between these two cohorts in terms of infant gender, gestational age, marital status, highest maternal educational level, family monthly income, paternal age and highest paternal educational level by χ^2 tests. The means of birth weights were 3060 (range 2221) and 3134 (range 2232) g for the study and comparison cohorts, respectively.

Table 2 describes the distribution of topical antiglaucoma medication during pregnancy. It shows that the majority of pregnant women (n = 189, 77.5%) were prescribed beta-blockers, and only seven were prescribed carbonic anhydrase inhibitors (2.9%) to control intraocular pressure. Table 2 also presents the means and ranges of birth weights, and percentage of LBW infants in relation to medication category.

Table 3 presents the percentage of LBW infants for women in the study and comparison cohorts. In total, 10.7% of the women in the study cohort and 6.2% in the comparison cohort had an LBW infant. We also separated the mothers in the study cohort into two groups: women who had been prescribed beta-blockers and women who had been prescribed drugs other than beta-blockers. In addition, details of the crude and adjusted odds ratios (OR) for the risk of LBW infants are also provided in table 3. As the table shows, after adjusting for potential confounders (characteristics of the infant (gender, parity, and gestational age), mother (age, the highest educational level, marital status, hypertension, and gestational diabetes), father (the highest educational level), parental age difference and family monthly income), the odds of LBW infants for women prescribed topical antiglaucoma medication during pregnancy was 1.63 times (95% CI 1.01 to 2.62) that of women in the comparison cohort. Interestingly, the adjusted odds ratio was as high as 2.15 (95% CI 1.05 to 5.00) for women prescribed medication other than beta-blockers compared with the comparison cohort. However, no significant difference in the risk of LBW infants was observed comparing women who had been prescribed beta-blockers during pregnancy and women in the comparison cohort (odds ratio = 1.48, 95% CI 0.86 to 2.56).

DISCUSSION

Using a population-based dataset from Taiwan, this study found that after adjusting for confounding factors, no significant difference in the risk of having LBW infants was observed, comparing women prescribed beta-blockers during pregnancy and women in the comparison cohort. However, there was a significantly higher risk of LBW infants for women prescribed topical antiglaucoma medications other than beta-blockers, as compared with the comparison group.

The FDA classifies all medications by safety for use in pregnancy. None of the antiglaucoma medications are classified as category A. Beta-blockers are classed as category C. There was a case report noting that topical timolol use in a pregnant woman was associated with fetal bradycardia and arrythmia.[8] Topical beta-blockers were the most frequently used antiglaucoma medication by pregnant women in our study (189 pregnant women, 77.5%). In Brauner *et al*'s study comprising 15 pregnant women with glaucoma (13 receiving topical medications), beta-blockers were also the most frequently used topical medication (11 patients).[2] This may be because obstetricians are most comfortable with beta-blockers because this class of medications is used to control hypertension in pregnant women.[9] In our study, topical beta-blockers were not associated with an increased risk of having LBW infants. Similarly, topical beta-blockers were not associated with any adverse effects in Brauner *et al*'s study.

While the FDA classifies most of the frequently used topical antiglaucoma agents as category C, sympathomimetics are the only topical antiglaucoma medications classified as category B. In this study, only 20 pregnant women were prescribed brimonidine tartrate (a sympathomimetic), and two of them (10%) had LBW infants. In Brauner *et al*'s study, four pregnant women were prescribed brimonidine tartrate, and no adverse effect was reported.[2] However, the small number of cases in our and Brauner *et al*'s studies does not allow a definite conclusion to be drawn about the fetal safety of brimonidine tartrate.

Although there are reports of association between the use of oral carbonic anhydrase inhibitors and sacrococcygeal teratoma and transient renal tubular acidosis in neonates,[10 11] no adverse effects associated with use of topical carbonic anhydrase inhibitors during pregnancy have been reported. In Brauner *et al*'s study, topical carbonic anhydrase inhibitors prescribed to

Table 2 Topical antiglaucoma medication prescribed to 244 women during pregnancy in relation to low birth weight outcomes

Category	No of patients (column %)	Birth weight (g) mean (range)	Low birth weight	
			Yes, n (row %)	No, n (row %)
Total	244	3060 (2221)		
Beta-blockers	189 (77.5)	3060 (2111)	17 (9.0)	172 (91.0)
Sympathomimetics	20 (8.2)	3020 (1632)	2 (10.0)	18 (90.0)
Carbonic anhydrase inhibitors	7 (2.9)	2961 (1510)	2 (28.6)	5 (71.4)
Cholinergics	12 (4.9)	3040 (1701)	3 (25.0)	9 (75.0)
Prostaglandin analogues	16 (6.6)	3067 (1520)	2 (12.5)	14 (87.5)

Table 3 Crude and adjusted odds ratios of having low birth weight infants for women who used topical antiglaucoma medication during pregnancy and women with no history of chronic disease, 2001~2003 (n = 2196)

	Mothers with no history of chronic disease		Mothers who used topical antiglaucoma medication (all categories) during pregnancy		Mothers who used topical beta-blockers during pregnancy		Mothers who used other topical antiglaucoma medication (all categories except beta-blocker category) during pregnancy	
	n = 1952		n = 244		n = 189		n = 55	
Variable	**No**	**%**	**No**	**%**	**No**	**%**	**No**	**%**
Low birth weight								
Yes	120	6.2	26	10.7	17	9.0	9	16.4
No	1832	93.8	218	89.3	172	91.0	46	83.6
Crude OR (95% CI)	1.00		1.67* (1.05 to 2.64)		1.51 (0.89 to 2.57)		2.23* (1.02 to 5.03)	
Adjusted OR† (95% CI)	1.00		1.63* (1.01 to 2.62)		1.48 (0.86 to 2.56)		2.15* (1.05 to 5.00)	

*$p<0.05$.
†Adjusted for infant's gender, parity, gestational age; maternal age, highest maternal educational level, maternal marital status, maternal hypertension, gestational diabetes; highest paternal educational level; parental age difference and family monthly income.
CI, confidence interval; OR, odds ratio.

four pregnant women were not associated with any adverse effects on the fetus.[2] However, in our study, two of the seven mothers prescribed topical carbonic anhydrase inhibitors (28.6%) had LBW infants. This percentage is much higher than that for the comparison group (6.2%). However, the small number of cases in both Brauner *et al*'s and our studies does not allow any firm conclusion to be made about the safety of topical carbonic anhydrase inhibitors use during pregnancy. Cholinergics use near term has been associated with neonatal hyperthermia, restlessness, seizure and diaphoresis.[12] In our study, three of 12 pregnant women prescribed topical cholinergics (25%) had LBW infants. In Brauner *et al*'s study, none of the three pregnant women using topical cholinergics had fetal complications.[2] Prostaglandins may cross the blood–placenta barrier and are known to be involved in stimulating uterine contraction. Use could theoretically induce miscarriage or premature labour. Therefore, historically, prostaglandin analogues have not been an option for first-line therapy.[6] Our present study also found that 12.5% of pregnant women prescribed prostaglandin analogues had LBW infants.

Findings of this study need to be interpreted in the context of the following limitations. First, information about patient compliance with drug use was not available. The presence of non-compliant patients in the study group would "dilute" or "mask" the difference between the study group and the comparison group. Second, data on some variables, such as smoking, unhealthy life styles and alcohol use, mothers' height and BMI, which may influence the risk of having LBW infants, were not available in our database. Third, data about whether punctual occlusion was executed on individual patients, which might influence the amount of systemic absorption of antiglaucoma medications,[13 14] were not available in our database. Fourth, although topical beta-blockers were not associated with an increased risk of having LBW infants, to label them completely safe for pregnancy, other side effects to the infant and mother should also be taken into consideration.

In summary, we found in this study that topical beta-blockers use was not associated with an increased risk of having LBW infants, while topical use of medications other than beta-blockers was associated with a significantly increased risk of having LBW infants. The significantly increased risk associated with antiglaucoma medications other than beta-blockers was likely influenced by the subgroups who used carbonic anhydrase inhibitors (two of seven had LBW infants, 28.6%) and who used cholinergics (three of 12 users had LBW infants, 25%). The number of patients in this group (users of antiglaucoma medications other than beta-blockers) was also relatively small. Therefore, the possibility of a chance finding cannot be excluded. The results of our study suggest that topical beta-blockers can be the first-line drugs for IOP control when considering medical treatment of glaucoma in pregnant women. In addition, punctual occlusion is recommended to minimise systemic absorption, as well as cooperation with an obstetrician to monitor the condition of the fetus and mother, to maximise the health of both.

Competing interests: None.

Provenance and peer review: Not commissioned; externally peer reviewed.

REFERENCES

1. **Qureshi IA,** Xi XR, Wu XD. Intraocular pressure trends in pregnancy and in the third trimester hypertensive patients. *Acta Obstet Gynecol Scand* 1996;**75**:816–19.
2. **Brauner SC,** Chen TC, Hutchinson BT, *et al*. The course of glaucoma during pregnancy: a retrospective case series. *Arch Ophthalmol* 2006;**124**:1089–94.
3. **Johnson SM,** Martinez M, Freedman S. Management of glaucoma in pregnancy and lactation. *Surv Ophthalmol* 2001;**45**:449–54.
4. **Kooner KS,** Zimmerman TJ. Antiglaucoma therapy during pregnancy—Part II. *Ann Ophthalmol* 1988;**20**:208–11.
5. **Kooner KS,** Zimmerman TJ. Antiglaucoma therapy during pregnancy—Part I. *Ann Ophthalmol* 1988;**20**:166–9.
6. **Coleman AL,** Mosaed S, Kamal D. Medical therapy in pregnancy. *J Glaucoma* 2005;**14**:414–16.
7. **Vaideanu D,** Fraser S. Glaucoma management in pregnancy: a questionnaire survey. *Eye* 2007;**21**:341–3.
8. **Wagenvoort AM,** van Vugt JM, Sobotka M, *et al*. Topical timolol therapy in pregnancy: is it safe for the fetus? *Teratology* 1998;**58**:258–62.
9. **Wide-Swensson D,** Montal S, Ingemarsson I. How Swedish obstetricians manage hypertensive disorders in pregnancy: a questionnaire study. *Acta Obstet Gynecol Scand* 1994;**73**:619–24.
10. **Ozawa H,** Azuma E, Shindo K, *et al*. Transient renal tubular acidosis in a neonate following transplacental acetazolamide. *Eur J Pediatr* 2001;**160**:321–2.
11. **Worsham F Jr,** Beckham EN, Mitchell EH. Sacrococcygeal teratoma in a neonate. *JAMA* 1978;**240**:251–2.
12. **Samples JR,** Meyer BS. Use of ophthalmic medications in pregnant and nursing women. *Am J Ophthalmol* 1988;**106**:616–23.
13. **Passo MS,** Palmer EA, Van Buskirk EM. Plasma timolol in glaucoma patients. *Ophthalmology* 1984;**91**:1361–3.
14. **Zimmerman TJ,** Kooner KS, Kandarakis AS, *et al*. Improving the therapeutic index of topically applied ocular drugs. *Arch Ophthalmol* 1984;**102**:551–3.