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Research report

Maternal bipolar disorder increased low birthweight and preterm births: A nationwide population-based study

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ABSTRACT

Objective: To investigate pregnancy outcomes, including low birthweight, preterm births, and small-for-gestational-age (SGA) among women with bipolar disorder, schizophrenia compared with women with no history of mental illness using nationwide population-based data.
Methods: This study linked the Taiwan National Health Insurance Research Dataset with the national birth certificate registry. A total of 528,398 singleton births between 2001 and 2003 were included; 337 were diagnosed with bipolar disorder. Multivariate logistic regression analyses were carried out to examine the relationship between maternal bipolar disorder, schizophrenia and the odds of low birthweight, preterm births, and SGA, after adjusting for characteristics of infant, mother and father.
Results: It shows that pregnant women with bipolar disorder were more likely to have LBW infants (9.8% vs. 5.7%), preterm births (14.2% vs. 6.9%) and SGA (22.3% vs. 15.7%) than pregnant women with no history of mental illness. The adjusted odds of low birthweight for women with bipolar disorder was 1.66 times (95% CI, 1.16–2.38) that of women with no history of mental illness. In terms of preterm births and SGA, the adjusted odds ratios were 2.08 (95% CI, 1.53–2.83) and 1.47 (95% CI, 1.14–1.91) respectively, for women with bipolar disorder, compared to their counterparts with no history of mental illness.
Conclusions: We conclude that women with bipolar disorder had increased risk of low birthweight, preterm births, and SGA than women without a history of mental illness. More active monitoring and early intervention to counter potential adverse pregnancy outcomes for pregnant women with bipolar disorder should be initiated.

1. Introduction

Mothers suffering from severe mental disorders are more likely to have adverse pregnancy outcomes. For example, Howard et al. reported that women with a history of psychotic disorders had a higher proportion of stillbirths and neonatal deaths compared with other women (Howard et al., 2004). Previous studies also found that schizophrenia women have increased risk of preterm delivery, stillbirth and low birthweight (LBW) (Nilsson et al., 2002; Rifkin et al., 1994; Bennedsen et al., 1999; Sacker et al., 1996). Besides schizophrenia, MacCabe et al. (2007) observed that mothers with affective disorders had elevated risk for preterm birth and small or growth-retarded babies. Webb et al. likewise reported higher risk of fatal birth defects associated with maternal affective disorder (Webb et al., 2007). However, few studies to date have focused specifically on women with bipolar disorder.

Jablensky et al. (2005) have examined the characteristics of infants born to women with schizophrenia, bipolar disorder, or major depression in Western Australia. They found an increased risk of obstetric complications among women with schizophrenia and women with bipolar disorder. However, no increased risk of LBW and preterm birth was

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observed among the women with bipolar disorder. It is still not clear whether the increased risk of adverse pregnancy outcomes associated with other severe mental disorders is also characteristic of bipolar disorder.

Therefore, this study aims to investigate pregnancy outcomes among women with bipolar disorder compared with women with no history of mental illness using nationwide population-based data. Understanding the association between maternal bipolar disorder and the risk of adverse pregnancy outcomes might help researchers understand possible genetic or environmental mechanisms linking maternal mental illness and pregnancy outcomes, as well as generate opportunities for policy makers and clinicians to provide optimal prenatal care.

2. Methods

2.1. Database

Two databases were used in this study. The first database was the National Health Insurance Research Dataset (NHIRD), published by the National Health Research Institute in Taiwan. The NHIRD includes inpatient and ambulatory care claims under Taiwan National Health Insurance (NHI) with over 21 million enrollees, representing around 96% of the island's population.

The second database used in this study is the birth certificate registry published by the Ministry of the Interior in Taiwan. The data on birth certificates includes birthdates of infants and their parents, gestational week at birth, infant birthweight, gender, parity, place of birth, parental educational level, and maternal marital status. With assistance from the Bureau of the NHI in Taiwan, mother's and infant's unique personal identification numbers provided links between the NHIRD and birth certificate data. Overall, 98.8% of fathers and 100.0% of mothers were identified on the birth certificate registry. All personal identifiers were encrypted by the Bureau of NHI before release to the researchers. Confidentiality assurances were addressed by abiding the data regulations of the Bureau of NHI.

2.2. Study sample

The sample for this research initially comprised all women with singleton births in Taiwan between January 1, 2001, and December 31, 2003 ($n=593{,}205$). We excluded women who had received treatment for any type of mental disorder (except schizophrenia and bipolar disorder: ICD-9-CM codes 295.XX, 296.0X, 296.1X, 296.4X, 296.5X, 296.6X, 296.7X, 296.80 or 296.89) within five years prior to the index delivery ($n=165$). Similarly, we excluded women whose husbands or partners received treatment for any type of mental disorder in the previous five years ($n=1093$) since prior studies have documented a significant association between paternal mental disorder and pregnancy outcome. Finally, we selected only the first delivery if a woman had more than one delivery during the study period. Ultimately, 528,891 women fulfilled our criteria and were included in our study.

2.3. Variables of interest

The outcome variables were preterm birth, small-for-gestational-age (SGA) and LBW. According the World Health Organization, the standard cut-off point for LBW in infants is 2500 g (<2500 g, ≥2500 g), and preterm birth was defined as birth occurring at a gestational age <37 weeks (World Health Organization, 1992). SGA is defined as birth weight below the tenth percentile for gestational age (Hsieh et al., 1991).

The independent variable of interest was whether or not a woman had bipolar disorder as identified from the catastrophic illness card issued by the Bureau of National Health Insurance. Women with schizophrenia were also selected as a comparison group. In Taiwan, once their diagnoses have been verified, patients with severe mental disorders (ICD-9-CM codes 290 and 293 through 297) may be issued a catastrophic illness card in order to reduce their financial burden. Since copayments for psychiatric care are waived for catastrophic illness cardholders, out of self interest, the majority of patients with serious mental disorders are likely to have applied for the card and to be recorded in the registry. Applications for catastrophic illness cards must be signed by a board-certified psychiatrist after diagnosis is verified through a series of visits.

We also adjusted for possible factors associated with preterm birth, SGA and LBW in the regression models. These include characteristics of the infant (gender and parity), mother (age, the highest educational level, marital status and whether gestation was complicated by hypertension or diabetes mellitus), father (age and the highest educational level) and family monthly income. Maternal ages were classified as <20, 20–34 and >34. Parity was grouped into the following categories: 1, 2, ≥3. Maternal and paternal education levels were categorized into four levels: elementary school or lower, junior high school, senior high school, college or above. Family monthly income was categorized according to four groups: <NT$15,000, NT15,000–NT30,000, NT30,001–NT50,000, ≥NT50,001.

2.4. Statistical analysis

The SAS statistical package (SAS System for Windows, Version 8.2) was used to conduct the analyses in this study. Pearson χ^2 tests were used to explore differences between women with bipolar disorder and women with no history of mental illness, in terms of characteristics of infant, mother and father. Multivariate logistic regression analyses were carried out to examine the relationships between maternal bipolar disorder and the odds of LBW, preterm birth and SGA, after adjusting for the characteristics of infant, mother and father. The relationships between maternal schizophrenia and these adverse pregnancy outcomes were also examined for comparison. Although maternal and paternal education levels are typically highly correlated with each other, we found their collinearity (correlation coefficient = 0.367) was tolerable and therefore both were kept in the regression model. In addition, we adjusted for age differences between parents in the regression model. A two-sided p-value of <0.05 was considered statistically significant for this study.

3. Results

Of the total sample of 528,891 pregnant women, 337 (0.064%) were diagnosed with bipolar disorder. Table 1 shows the details of the distribution of the characteristics of infants, fathers and parturients, separated into those with bipolar disorder, those with schizophrenia and those with no history of mental illness. It shows that pregnant women with bipolar disorder were more

Table 1
Comparisons of women with bipolar disorder and women with no history of mental illness in relation to sociodemographic characteristics and gestational comorbid medical disorders in Taiwan, 2001–2003 ($n = 528,891$).

Variable	Women with bipolar disorder		Women with schizophrenia		Women with no history of mental illness	
	Total no.	%	Total no.	%	Total no.	%
Infant characteristics						
Birthweight (g)						
<2500	33	9.8	49	9.9	30,055	5.7
≥2500	304	90.2	444	90.1	498,006	94.3
Gender						
Male	180	53.4	275	55.8	276,041	52.3
Female	157	46.6	218	44.2	252,020	47.7
Parity						
1	160	47.5	253	51.3	277,765	52.6
2	126	37.4	151	30.6	175,897	33.3
3 or more	51	15.1	89	18.1	74,399	14.1
Gestational age (week)						
<37	48	14.2	49	9.9	36,245	6.9
≥37	289	85.8	444	96.1	491,816	93.1
Small for gestational age						
Yes	75	22.3	115	23.3	82,699	15.7
No	262	77.7	378	76.7	445,362	84.3
Maternal characteristics						
Age						
<20	11	3.3	9	1.8	19,893	3.8
20–34	282	83.7	400	81.1	456,654	86.5
>34	44	13.1	84	17.0	51,514	9.8
Education level						
Elementary school or lower	7	2.1	18	3.7	10,284	2.0
Junior high school	89	26.4	152	30.8	83,669	15.8
Senior high school	207	61.4	291	59.0	358,640	67.9
College or above	34	10.1	32	6.5	75,468	14.3
Marital status						
Married	316	93.8	452	91.7	512,776	97.1
Other	21	6.2	41	8.3	15,285	2.9
Gestational diabetes						
Yes	0	0	3	0.6	940	0.2
No	337	100	490	99.4	527,121	99.8
Gestational hypertension						
Yes	5	1.5	1	0.2	2,800	0.5
No	332	98.5	492	99.8	525,261	99.5
Family monthly income						
<NT$15,000	107	31.8	129	26.2	163,219	30.9
NT$15,000–30,000	87	25.8	173	35.1	112,603	21.3
NT$30,001–50,000	100	29.7	157	31.9	152,268	28.8
>NT$50,000	43	12.8	34	6.9	99,971	18.9
Paternal characteristics						
Age						
<30	124	36.8	125	25.4	204,382	38.7
30–34	122	36.2	170	34.5	196,646	37.2
>34	91	27.0	198	40.2	127,033	24.1
Education level						
Elementary school or lower	8	2.4	37	7.5	8130	1.5
Junior high school	88	26.1	161	32.7	96,681	18.3
Senior high school	203	60.2	267	54.2	326,915	61.9
College or above	38	11.3	28	5.7	96,335	18.2

likely to have LBW infants (9.8% vs. 5.7%), preterm births (14.2% vs. 6.9%) and SGA (22.3% vs. 15.7%) than pregnant women with no history of mental illness. Pearson χ^2 also shows that there were significant differences between women with bipolar disorder and women with no history of mental illness in terms of maternal age ($p = 0.049$), highest maternal educational level ($p < 0.001$), marital status ($p < 0.001$), gestational hypertension ($p = 0.016$), family monthly income ($p = 0.018$) and highest paternal educational level ($p < 0.001$) (not shown on Table 1).

Table 2 describes the distribution and crude odds ratios of LBW, preterm birth and SGA of the maternal bipolar disorder and non-mental disorder groups. The regression analysis shows that women with bipolar disorder were more likely to have LBW infants, preterm births and SGA babies than women with no history of mental illness.

Details of the adjusted odds ratios for the risk of LBW, preterm birth and SGA by maternal bipolar disorder are provided in Table 3. As the table shows, following adjustment

Table 2
Distributions of LBW, preterm birth and SGA among women with bipolar disorder, schizophrenia, and no history of mental illness, 2001–2003 ($n = 528,891$).

Variable	Low birthweight			Preterm birth			Small for gestational age		
Women with	Yes,	No	OR, 95% CI	Yes	No	OR, 95% CI	Yes	No	OR, 95% CI
	n (row %)	*n* (row %)		*n* (row %)	*n* (row %)		*n* (row %)	*n* (row %)	
Bipolar disorder	33 (9.8)	304 (90.4)	1.80** (1.26–2.58)	48 (14.2)	289 (85.8)	2.26*** (1.66–3.06)	75 (22.3)	262 (77.7)	1.54*** (1.19–2.00)
Schizophrenia	49 (9.9)	444 (90.1)	1.83*** (1.36–2.46)	49 (9.9)	444 (90.1)	1.50* (1.12–2.01)	115 (23.3)	378 (76.7)	1.64*** (1.33–2.02)
No history of mental illness	30,055 (5.7)	498,006 (94.3)	1.00	36,245 (6.9)	491,816 (93.1)	1.00	82,699 (15.7)	445,362 (84.3)	1.00

Note: * indicates $p<0.05$; ** indicates $p<0.01$; *** indicates $p<0.001$.
Odds ratios (OR) are unadjusted.

for the infant's gender, parity, maternal age, highest paternal and maternal educational level (separately), mothers' marital status and family monthly income, the odds of LBW for women who had bipolar disorder was 1.66 times (95% CI = 1.16–2.38) that of women without bipolar disorder. In terms of preterm births and SGA, the adjusted odds ratios were 2.08 (95% CI, 1.53–2.83) and 1.47 (95% CI, 1.14–1.91) respectively, for women with bipolar disorder compared to their counterparts with no history of mental illness.

In the comparison group of women with schizophrenia, the odds ratios were only significant for LBW and SGA, but not for preterm births.

4. Discussion

This nationwide population-based study found that women with bipolar disorder had increased risk of adverse pregnancy outcomes: the odds of LBW, preterm birth and SGA for these women were 1.66, 2.08 and 1.47 times, respectively, greater than for women with no history of mental illness, after maternal, paternal and infant characteristics were taken into account. Our findings accord with previous studies on women with schizophrenia that indicated a higher risk of premature birth or small or growth-retarded babies (Howard et al., 2004; Nilsson et al., 2002; Rifkin et al., 1994; Bennedsen et al., 1999; Sacker et al., 1996).

A study by MacCabe et al. (2007) previously reported that mothers with affective disorder had elevated risk of giving birth to preterm (OR = 2.67) and LBW babies (OR = 2.22) using the Swedish Medical Birth Register between 1983 and 1997. Despite limiting our study sample specifically to bipolar disorder, our findings remained consistent with theirs; only the risk magnitude of the OR differed. Conversely, a similar study by Jablensky et al. (2005) reported no differences in LBW and preterm births comparing women with bipolar disorder and a comparison group of women who gave birth in Western Australia from 1980 to 1992. They even found that women who were not in the psychiatric case register had higher preterm birth rates than women with bipolar disorder (7.6% vs. 6.2%), although this relationship did not reach a significant level. The different findings from these two studies may be difficult to explain due to different study populations, regions, and eras. However, since all explanations for LBW among mothers with schizophrenia offered by Jablensky et al. could also apply to mothers with bipolar disorder, our results may be closer to the facts. As they suggested, more women with severe mental disorders are now capable of living in the community and having children, thus the growing number of mothers with bipolar disorder may drive up the possibility of having LBW infants, accelerating the trend to a visible level in our updated study.

Mechanisms underlying the increased risk of adverse pregnancy outcomes for women with bipolar disorder remain unclear. However, a recent literature review by Walker and colleagues concluded that a number of susceptibility genes are shared between schizophrenia and bipolar disorder (Walker et al., 2002; Laursen et al., 2007). Growing evidence of an etiologic overlap between schizophrenia and bipolar disorder suggest that the possible underlying mechanisms for adverse pregnancy outcomes may be the same for both disorders. One study by Bennedsen (1998) summarized possible risk factors for

Table 3
Adjusted Odds ratios of LBW, preterm birth and SGA for women with bipolar disorder or schizophrenia compared to women with no history of mental illness in Taiwan ($n = 528,891$).

Variable	Low birthweight	Preterm birth	Small for gestational age
	Adjusted OR, 95% CI	Adjusted OR, 95% CI	Adjusted OR, 95% CI
Women with			
Bipolar disorder	1.66** (1.16–2.38)	2.08*** (1.53–2.83)	1.47** (1.14–1.91)
Schizophrenia	1.62** (1.20–2.18)	1.33 (0.99–1.79)	1.52*** (1.23–1.87)
No history of mental illness	1.00	1.00	1.00
Maternal characteristics			
Age (years)			
<20	1.00	1.00	1.00
20–34	0.75*** (0.72–0.80)	0.81*** (0.77–0.85)	0.73*** (0.71–0.76)
>34	0.92* (0.86–0.99)	1.01** (1.03–1.17)	0.74*** (0.71–0.79)
Education level			
Elementary school or lower	1.37*** (1.28–1.48)	1.25*** (1.1701.34)	1.23*** (1.17–1.29)
Junior high school	1.22*** (1.18–1.26)	1.18*** (1.14–1.21)	1.15*** (1.12–1.17)
Senior high school	1.00	1.00	1.00
College or above	0.92*** (0.88–0.96)	0.95** (0.91–0.98)	0.90*** (0.87–0.92)
Marital status			
Married	0.61*** (0.58–0.64)	0.66*** (0.63–0.70)	0.66*** (0.63–0.68)
Others	1.00	1.00	1.00
Gestational hypertension			
Yes	3.33*** (3.12–3.80)	2.81*** (2.55–3.10)	2.15*** (1.98–2.34)
No	1.00	1.00	1.00
Infant characteristics			
Gender			
Male	0.78*** (0.77–0.80)	1.21*** (1.19–1.24)	0.71*** (0.70–0.72)
Female	1.00	1.00	1.00
Parity			
1	1.00	1.00	1.00
2	0.79*** (0.77–0.81)	1.05*** (1.03–1.08)	0.82*** (0.80–0.83)
3 or more	0.80*** (0.77–0.83)	1.19*** (1.15–1.23)	0.78*** (0.77–0.80)
Family monthly income			
<NT$15,000	1.00	1.00	1.00
NT$15,000–30,000	0.97 (0.94–1.01)	0.99 (0.96–1.02)	0.94***(0.92–0.96)
NT$30,001–50,000	0.91*** (0.88–0.94)	0.96* (0.94–0.99)	0.89*** (0.88–0.91)
>NT$50,000	0.88*** (0.84–0.91)	0.94*** (0.91–0.97)	0.85*** (0.83–0.87)
Age difference (paternal age–maternal age)	1.00 (0.99–1.01)	1.00 (0.99–1.01)	1.00 (0.99–1.01)
Paternal characteristics			
Education level			
Elementary school or lower	1.31*** (1.21–1.43)	1.19*** (1.10–1.28)	1.28*** (1.21–1.35)
Junior high school	1.17*** (1.13–1.20)	1.10*** (1.07–1.13)	1.14*** (1.11–1.16)
Senior high school	1.00	1.00	1.00
College or above	0.88*** (0.85–0.92)	0.93*** (0.90–0.97)	0.90*** (0.88–0.93)

Note: * indicates $p<0.05$; ** indicates $p<0.01$; *** indicates $p<0.001$.
Note: * indicates $p<0.05$; ** indicates $p<0.01$; *** indicates $p<0.001$.
In the fully adjusted model, maternal age, education level, marital status, and gestational hypertension, and infant's gender and parity, plus family monthly income, parental age difference, and paternal education level were included.

low birth weight and preterm birth among schizophrenia women. She has categorized potential risk factors as follows: smoking, substance abuse, including alcohol, cannabinoids and other illicit drugs, caffeine consumption, socioeconomic factors, parity and maternal age, nutritional factors, maternal physical illness and antenatal care. The higher risks of LBW and SGA babies among schizophrenic women observed in this study may lend support to a common underlying mechanism.

In addition, Jablensky et al. (2005) have proposed that the increased risk of adverse pregnancy outcomes among women with affective disorder can be explained by the clustering of adverse maternal characteristics. Women with affective disorders are more likely to have unhealthy lifestyles, including poor diet, a lack of exercise and obesity, largely attributable to their socioeconomic disadvantages and to lack of adequate social support. These reproductive hazards among women with bipolar disorder could increase their risk of adverse pregnancy outcomes.

However, in the current study, even after adjusting for socioeconomic factors, parity, maternal age, and maternal physical illness, the relationship between increased risk of adverse pregnancy outcomes and bipolar disorder remained. It seems that these factors may not be the major determinants of adverse pregnancy outcomes among women with bipolar disorder.

Smoking is likely to be one explanation for the relationship. One study by Wilens et al. found that bipolar disorder was associated with a significant age-adjusted risk for cigarette

smoking (hazard ratio = 12.3) (Wilens et al., 2008). Another study by Gonzalez-Pinto et al. even indicated that bipolar disorder (in both genders) was significantly associated (OR = 4.4) with heavy smoking (more than 1 pack per day) (Gonzalez-Pinto et al., 1998). However, data on cigarette smoking was not available in our dataset. But the study by MacCabe et al. (2007) did show that the relationship between mothers with affective disorder and elevated risk of adverse pregnancy outcomes persists even after adjusting for smoking. Therefore, smoking may not be the sole cause of this relationship.

The treatment for bipolar disorder itself, whether persistent or discontinued, during pregnancy may be another potential factor contributing to this relationship. At present, it is still difficult to estimate the risks and benefits of taking such medication during pregnancy, due to inadequate data (Wisner et al., 2000).

The strengths of this study include its use of nationwide population-based datasets linking the NHIRD with birth certificates and the adjusting for important characteristics of mother, father and infant. However, the findings of this study should be interpreted within the context of three limitations. First, we identified mothers diagnosed with bipolar disorder from the registry of catastrophic illness released by the Bureau of the NHI, potential sampling bias existed, such as a financial incentive for bipolar patients with low socioeconomic status to apply for the catastrophic illness card. Secondly, with respect to validity and reliability, there was no standardized diagnostic algorithm of bipolar disorder in service claims data. In addition, this dataset did not allow us to account for differences in the severity of bipolar disorder among patients. Thirdly, information on mothers' smoking history, substance abuse, alcohol consumption, nutrition and body mass index are not available through our datasets.

Despite these limitations, this study found that women with bipolar disorder had increased risk of LBW and preterm births than women without bipolar disorder, after adjusting for potential confounders. Clinicians should be aware of the increased risk of adverse pregnancy outcomes among these women. More active monitoring and early intervention to counter potential LBW and preterm births should be initiated for women with bipolar disorder. In addition, further studies are needed to elucidate the underlying mechanisms linking bipolar disorder among mothers and fetal development.

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Nothing declared.

Conflict of interest

No conflict declared.

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