Association between the use of antidepressants and the risk of preterm birth among pregnant women with depression: a retrospective cohort study in Taiwan

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► Additional material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/jim-2020-001683).

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Accepted 9 February 2021
Published Online First 1 March 2021

To cite: Chen L-F, Lin C-E, Chung C-H, *et al*. *J Investig Med* 2021;**69**:999–1007.

ABSTRACT

Our study was aimed to investigate the association between the use of antidepressants and the risk of preterm birth in pregnant women who have had perinatal depression. We extracted data from the Taiwanese National Health Insurance Research Database (NHIRD) and analyzed them using multivariate Cox proportional hazard regression models. Identified from the NHIRD, we matched 1789 women aged 18–55 years who were using antidepressants during pregnancy and 1789 women who were experiencing depression but who were not using antidepressants during pregnancy for age, index date, and medical comorbidities. We enrolled the women in our study, which we conducted using 12 years' worth of data between 2000 and 2012, and then followed up individually with them for up to 1 year to identify any occurrence of preterm birth. Results highlighted that, compared with the women with perinatal depression who were not using antidepressants during pregnancy, the women taking antidepressants had a 1.762-fold risk of preterm birth (adjusted HR=1.762, 95% CI 1.351 to 2.294, p<0.001). The use of antidepressants in women with perinatal depression may increase the risk of preterm birth. However, the decision to start, stop, or change the use of antidepressants during pregnancy requires evaluating the risks of treatment versus untreated depression for both mother and child.

Significance of this study

What is already known about this subject?

- Pregnant women who are taking antidepressants are often associated with having adverse perinatal outcomes, especially preterm birth.

What are the new findings?

- Overall, pregnant women taking antidepressants had a higher risk of preterm birth than did the control women, with a dose–response effect.
- For type of antidepressants, women taking serotonin norepinephrine reuptake inhibitors, tricyclic antidepressants, and others had a similar risk of preterm birth as compared with those taking selective serotonin reuptake inhibitors.
- Women who had used antidepressants during their third trimester had the highest risk of preterm birth.

How might these results change the focus of research or clinical practice?

- Indication bias cannot be completely ruled out in our study, and future studies are warranted to confirm our findings.

INTRODUCTION

In Western countries, the incidence rate of depressive symptoms during pregnancy is approximately 7.5%–51%,[1] which is often underestimated in obstetrics and gynecology or primary care settings.[2] Pregnant women with a history of depression tend to have a higher risk of recurrence, especially after discontinuation of antidepressant therapy during pregnancy.[3] Maternal depression is associated with undesirable perinatal outcomes, including preterm birth.[4–8]

On the other hand, pregnant women who are taking antidepressants are often associated with having adverse perinatal outcomes, especially preterm birth.[9–13] Insights into whether these associations are due to causal mechanisms (eg, poorly functioning serotonin signaling)[14] or other alternative explanations (eg, confounding by indication for such treatment) remains unclear. Therefore, treating women with depression during pregnancy is challenging because the benefits and risks associated with antidepressants are still poorly understood.[15–18]

Randomized clinical trials have not yet been able to test the safety of using antidepressants during pregnancy despite the fact that treatment of depression during pregnancy is clinically allowed.[16] Therefore, analyzing a large observational cohort may determine whether the use of antidepressants in pregnant women can increase the risk of preterm birth. Therefore, our study

evaluates the risk of preterm birth using the Taiwanese National Health Insurance Research Database (NHIRD).

METHODS

Database

This retrospective cohort study used the NHIRD database, which covers nearly 99% of residents in Taiwan and is offered by the Data Science Center of the Ministry of Health and Welfare. The dataset includes registration and medical claims for 1,000,000 randomly sampled individuals from a total of 25.68 million beneficiaries registered in the NHIRD. It also includes detailed information regarding the health insurance system between 2000 and 2013.

Inclusion criteria for study chorts

Because the NHIRD was launched in 1995, patients' medical claims before that year have remained unrecorded, and therefore, information on pregnant women with perinatal depression before that time is unavailable. Because gravidity may happen 3 months before and during the study period, we chose pregnant women aged 18–55 years (*International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM), codes 642.0–642.7, 642.9, 643.0–643.2, 643.8–643.9, 645.1–645.2, 646.1–646.2, 646.4–646.9, 647.0–647.6, 647.8–647.9, 648, and 650) with perinatal depression (ICD-9-CM codes 296.2–296.3 and 311; *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR[19]): major depressive disorder, single episode or recurrent, and depressive disorder not otherwise specified) who were diagnosed with depression within 90 days before the date of their pregnancy test (not necessarily their first pregnancy in life).

We obtained our study cohort (n=23,889) using the dates from January 1, 2000, to December 31, 2013. We defined the cohort's index date as the first day of pregnancy on the basis of medical claims. Exclusion criteria included[1] women who have had a previous preterm birth (ICD-9-CM codes 644.0–644.2 and 765.0–765.1)[2]; pregnant women with a history of abortion (ICD-9-CM codes 630–639; 81001C–81002C, 81006C–81007C, 81 008B, 81009C–81010C, 81 012B, 81 020B, 81 022B, and 81030C–81031C), delivery (ICD-9-CM codes 650–659; OP73.59, OP73.6, OP74.0–OP74.1; 81004C–81005C, 81017C–81019C, 81024C–81026C, 81028C–81029C, and 81 034C), or mortality at baseline[3]; women diagnosed with schizophrenia (ICD-9-CM code 295), bipolar disorder (ICD-9-CM codes 296.4–296.7), or substance abuse or dependence (ICD-9-CM codes 303–305); and[4] women using mood stabilizers (n=13,275). After the exclusion process, we selected 10 614 pregnant women with perinatal depression, of which 1789 women had antidepressant treatment and 8825 women did not have such treatment 90 days before the date of their first pregnancy test and between the first and last dates of their pregnancy tests during the study period.

After the onefold propensity score matched by age, index date, sociodemographic variables, and medical comorbidities shown in the section Potential Confounding Variables, our study included 1789 patients undergoing antidepressant treatment and 1789 patients with no antidepressant treatment 90 days before the date of their first pregnancy test and between the first and last dates of their pregnancy tests during the study period.

To achieve full diagnostic validity, we specified that the diagnoses of any form of depression would appear at least twice for consecutive outpatient or once for inpatient medical records. The flowchart of the patient selection process is provided in figure 1.

Antidepressant exposure definition

The types of antidepressants we studied included selective serotonin reuptake inhibitors (SSRIs; fluoxetine, fluvoxamine, sertraline, and paroxetine), serotonin norepinephrine reuptake inhibitors (SNRIs; venlafaxine and duloxetine), tricyclic antidepressants (TCAs; imipramine, clomipramine, desipramine, trimipramine, amitriptyline, nortriptyline, amoxapine, doxepin, maprotiline, and protriptyline), and others (bupropion, mirtazapine, and trazodone). We used the defined daily dose (DDD) to describe certain amounts of antidepressants, which we calculated using the following formula: (total amount of the individual drug)/(DDD of the drug)=number of DDDs. The daily dose of each antidepressant was based on the international standard DDD (Anatomical Therapeutical Chemical (ATC)/DDD Index 2020; http://www.whocc.no/atc ddd index/; accessed May 8, 2020). Cumulative DDDs, that is, the sum of DDDs for any antidepressant, served as an index of the cumulative dosage of the antidepressant. Because the NHIRD is a medical claims database, the DDD can represent only the number of drug prescription days rather than actual use; therefore, we could not assess the duration or continuation of antidepressant usage precisely. Many previous pharmacological studies have adopted this method as well.[20]

Main outcome measures

We followed up the two groups of women individually for up to 1 year to compare the risk of preterm birth. We considered the date of preterm birth diagnosis (<37 completed weeks of gestation; ICD-9-CM codes 644.0–644.2 and 765.0–765) made for the first time during either the follow-up period or the end of the study (December 31, 2013) to be the study's endpoint.[21]

Potential confounding variables

Age, income-related insurance premium, hospital type, and urbanization levels constituted the sociodemographic variables of this study. We also assessed potential baseline clinical factors related to preterm birth to identify comorbidities, including multiple gestation (ICD-9-CM codes 651.0–651.6, 651.8–651.9, 652.6, and 659.4), diabetes mellitus (ICD-9-CM code 250), hypertension (ICD-9-CM codes 401.0–01.1, 401.9, 402.0–402.1, 402.9, 403.0–403.1, 403.9, 404.0–404.1, 404.9, 405.0–405.1, 405.9, 642.0–642.3, 642.7, 642.9, 760.0, and 796.2), dyslipidemia (ICD-9-CM code 272), uteroplacental ischemia or hemorrhage (ICD-9-CM codes 656.7 and 656.8), reproductive tract infection (ICD-9-CM codes 647.9, 658.4, 659.3, 670.0, 671.2, 671.5, 671.8–671.9, 674.0, 674.8–674.9, 761.1, and 762.0), pre-eclampsia (ICD-9-CM codes 642.4–624.5), eclampsia (ICD-9-CM codes 642.6–642.7), placenta previa (ICD-9-CM codes 641.0 and 641.00–641.03), abruptio placenta (ICD-9-CM codes 641.2,

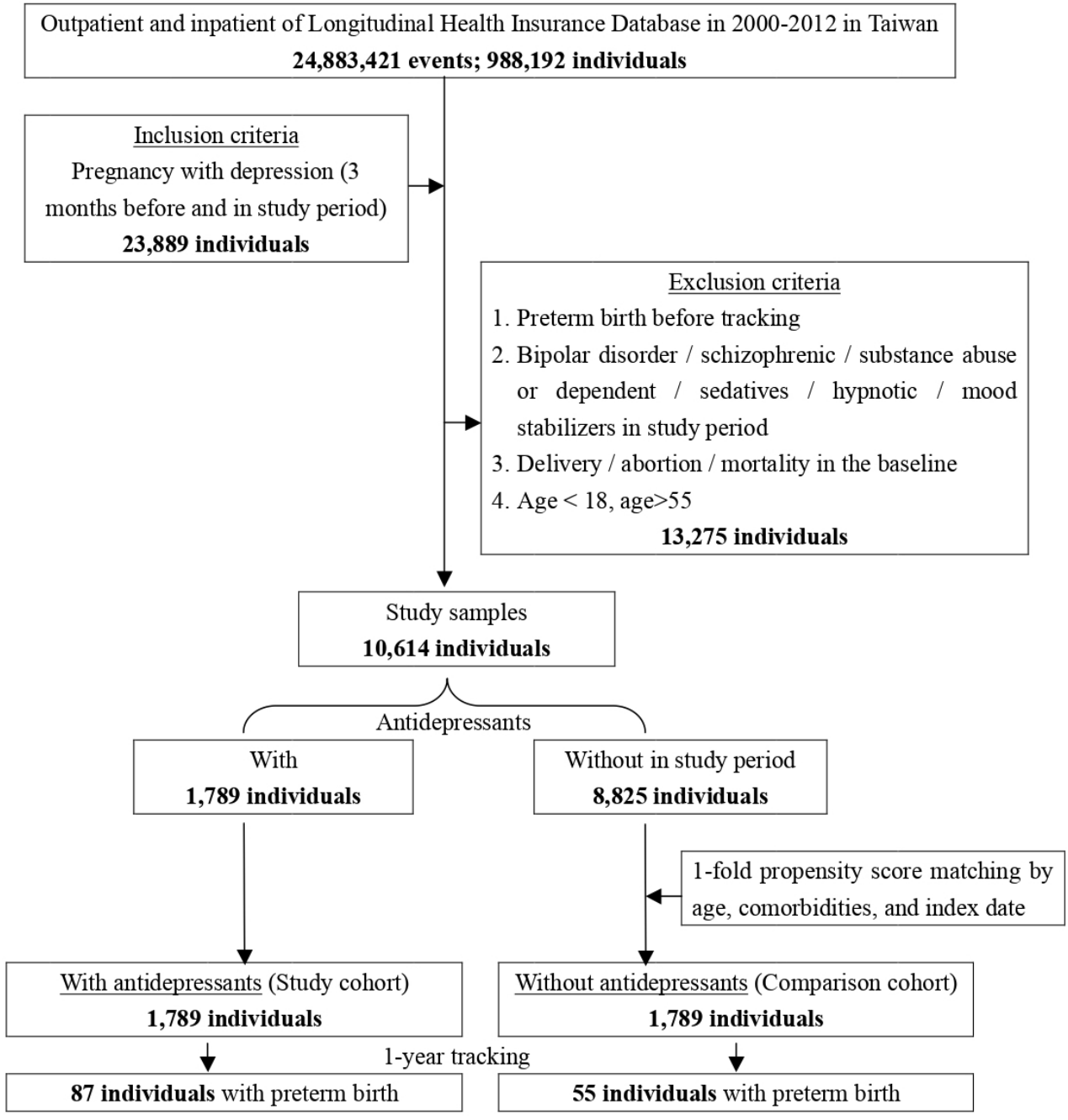

Figure 1 Flowchart of the patient selection process.

641.20–641.23), polycystic ovaries (ICD-9-CM code 256.4), hypogonadism (ICD-9-CM code 256.39), hypergonadism (ICD-9-CM code 256.1), pregnancy with history of infertility (ICD-9-CM code V23.0), morbid obesity or being overweight (ICD-9-CM codes 278.01 and 278.02), and anxiety disorders ((ICD-9-CM code 300); DSM-IV-TR[19]: panic disorder, specific phobia, agoraphobia, generalized anxiety disorder, obsessive–compulsive disorder, and anxiety disorder not otherwise specified).[22–30]

Statistical analysis

For between-group comparisons, we used the independent t-test for continuous variables and Pearson's χ^2 test for nominal variables. To estimate the cumulative incidence risk of preterm birth in both cohorts, we conducted a survival analysis using the Kaplan-Meier method, with significance based on the log-rank test. Furthermore, we measured the crude HR and adjusted HR (aHR), respectively, with a 95% CI for developing preterm birth, using a Cox proportional regression model before and after adjusting for demographic data and medical comorbidities, including age, income-related insurance premium, hospital types, urbanization levels, nulliparity or multiparity, multiple gestation, diabetes mellitus, hypertension, dyslipidemia, uteroplacental ischemia or hemorrhage, reproductive tract infection, pre-eclampsia, eclampsia, placenta previa, abruptio

placenta, polycystic ovaries, hypogonadism, hypergonadism, pregnancy with history of infertility, morbid obesity or being overweight, and anxiety disorders.

We used a doubly robust estimation for determining p values and 95% CIs in all the Cox regression models.[31] We also conducted stratified analyses to compare the effects of sociodemographic variables, medical comorbidities, types and dosage of antidepressants, and pregnancy trimesters on preterm birth development. We performed data processing and statistical analyses using SPSS software V.22.

RESULTS

During the defined follow-up period, 87 (4.86%) individuals in the study cohort (those undergoing antidepressant treatment) and 55 individuals (3.07%) in the control cohort (those not undergoing antidepressant treatment) had preterm birth (p<0.001). The mean age of the study cohort was 40.60±10.67 years, whereas that of the matched control cohort was 40.55±10.61 years (p=0.888). Other characteristics were comparable between the study and matched control cohorts (table 1).

Table 2 highlights that women undergoing antidepressant treatment in their third trimester (aHR=2.009, 95% CI 1.675 to 2.587, p<0.001) had the highest aHR, followed by those in their first trimester (aHR=1.650, 95% CI 1.248 to 2.132, p<0.001) and those in their second trimester (aHR=1.431, 95% CI 1.043 to 1.981, p=0.007). For dosage, women treated with SSRIs had a dose–response effect on the risk of preterm birth. Likewise, women treated with SNRIs, TCAs, and other types of antidepressants all had a dose–response effect on preterm birth (table 3). For type of antidepressants, women taking SNRIs, TCAs, and others had a similar risk of preterm birth as compared with those taking SSRIs (table 4).

Online supplemental table S1 shows the incidence and aHR of preterm birth stratified by covariates in the cohorts. The incidence rate of preterm birth in 87 patients in the study cohort was 5.31 per 10^3 person-months (PMs), whereas that of 55 patients in the control cohort was 3.36 per 10^3 PMs. Thus, the study cohort had a significantly higher preterm birth incidence than did that of the control cohort (p<0.001). After adjusting for potential confounder bias, including variables mentioned in the section Potential Confounding Variables, our results highlighted that antidepressant treatment was associated with a 1.762-fold risk of preterm birth (aHR=1.762, 95% CI 1.351 to 2.294, p<0.001).

In the stratified analyses, women aged 35–55 years (aHR=2.481, 95% CI 1.903 to 3.231, p<0.001) had a greater risk of preterm birth compared with those who were younger. Primiparous women (aHR=1.805, 95% CI 1.384 to 2.350, p<0.001) also had a higher risk of preterm birth compared with multiparous women (aHR=1.698, 95% CI 1.301 to 2.111, p<0.001). In addition, women undergoing antidepressant treatment who also had comorbidities such as anxiety disorder (aHR=1.834, 95% CI 1.405 to 2.386, p<0.001), multiple gestation (aHR=4.725, 95% CI 3.622 to 6.148, p<0.001), diabetes mellitus (aHR=9.425, 95% CI 7.288 to 12.648, p<0.001), hypertension (aHR=3.011, 95% CI 2.318 to 3.975, p<0.001), dyslipidemia (aHR=7.101, 95% CI 5.483 to 9.120, p<0.001), or reproductive tract infection (aHR=3.421, 95% CI 2.638 to 4.422, p<0.001) had a higher aHR than did those who had no comorbidities (online supplemental table S1).

Compared with the women who were not taking antidepressants, the risk of preterm birth of ≤35 gestational weeks (aHR=1.820, 95% CI=1.395–3.093, p<0.001) was higher than that of <37 gestational weeks (aHR=1.762, 95% CI 1.351 to 2.294, p<0.001) among the women taking antidepressants (online supplemental table S2). The risk of preterm birth (aHR=1.510, 95% CI 1.137 to 1.982, p<0.001) in the original cohort was similar to that (aHR=1.762, 95% CI 1.351 to 2.294, p<0.001) in the matched cohort (Table S3). According to the Kaplan-Meier survival analysis (figure 2), the study cohort had a significantly higher cumulative incidence risk of preterm birth as compared with the control cohort (log-rank test, p<0.001).

DISCUSSION

Our study reveals that women with perinatal depression who were receiving antidepressant treatment during pregnancy had a significantly increased risk of preterm birth. The overall incidence rate of preterm birth was 5.31 and 3.36 per 10^3 PMs in the study and control cohorts, respectively (p<0.001). These results are consistent with other recent observational data.[9–13]

In studies controlling for maternal depression, no link was found between antidepressant exposure and preterm birth.[32–34] Women with depression or who were treated may not have been appropriately coded,[35] and confirming that women actually took the medicines prescribed is quite difficult. Furthermore, women with perinatal depression during pregnancy may manifest differently in Chinese culture, such as having more complaints of neurasthenia, somatization, or somatic symptoms than expressing depression directly. Thus, many users of antidepressants probably express atypical symptoms of depression and are not diagnosed with depressive disorder, which is also true of women during pregnancy.[36] Therefore, a residual confounding effect may exist in the present study if we restrict study patients only to women with depression during pregnancy. Without adjusting these factors, all would likely have bias results to the null.

The estimated global preterm rate for 2014 was 10.6%, equating to an estimated 14.84% million live preterm births in that year. More than 80% of these births occurred in Asia and in sub-Saharan Africa.[37] Compared with the annual preterm birth rate in the general population in Taiwan, which ranged from 3.33% in 2004 to 5.11% in 2013,[21] the overall prevalence of preterm births was 4.86% in the pregnant women with perinatal depression receiving antidepressant treatment in our study. Some possible explanations exist for the finding that Taiwanese women with depression have a preterm rate lower than the global rate. One major reason is the different measurement methods for gestational age that confound estimation of preterm birth rates. Ultrasound early in pregnancy for measurement of fetal-crown-rump is considered the gold standard for assessment of gestational age in Taiwan.[38] However, less-accurate methods, such as last menstrual period, symphysis–fundal height measurement, postnatal examination of the baby, or birth weight, are often used, particularly in low-income and

Table 1 Characteristics of study patients at baseline

Variables	With antidepressants		Without antidepressants (unmatched)		P value*	Without antidepressants (onefold matching)		P value†
	n	%	n	%		n	%	
Total	1789		8825			1789		
First pregnancy					<0.001			0.999
Yes	894	49.97	5592	63.37		894	49.97	
No	895	50.03	3233	36.63		895	50.03	
Age (years)	40.60±10.67		36.21±11.84		<0.001	40.55±10.61		0.888
Age group (years)					<0.001			0.999
18–34	358	20.01	4228	47.91		358	20.01	
35–55	1431	79.99	4597	52.09		1431	79.99	
Insured premium (new Taiwan dollar)					<0.001			0.993
<18,000	1612	90.11	7351	83.30		1610	89.99	
18,000–34,999	124	6.93	862	9.77		125	6.99	
≥35,000	53	2.96	612	6.93		54	3.02	
Comorbidities								
Anxiety disorder	786	43.94	4142	46.93	0.110	787	43.99	0.973
Multiple gestation	6	0.34	98	1.11	0.002	5	0.28	0.763
Diabetes mellitus	220	12.30	2156	24.43	<0.001	221	12.35	0.959
Hypertension	318	17.78	2978	33.75	<0.001	319	17.83	0.985
Dyslipidemia	136	7.60	1814	20.56	<0.001	136	7.60	0.999
Uteroplacental ischemia and hemorrhage	0	0	11	0.12	0.230	0	0	–
Reproductive tract infection	6	0.34	19	0.22	0.296	6	0.34	0.999
Pre-eclampsia	3	0.17	9	0.10	0.439	2	0.11	0.654
Eclampsia	0	0	7	0.08	0.610	0	0	–
Placenta previa	3	0.17	16	0.18	0.901	3	0.17	0.999
Abruptio placenta	0	0	0	0	–	0	0	–
Polycystic ovaries	2	0.11	4	0.05	0.268	1	0.06	0.564
Hypogonadism	0	0	1	0.01	0.653	0	0	–
Hypergonadism	0	0	0	0	–	0	0	–
Pregnancy with history of infertility	3	0.17	13	0.15	0.743	2	0.11	0.654
Morbid obesity or overweight	1	0.06	8	0.09	0.645	1	0.06	0.999
Location					<0.001			0.997
Northern Taiwan	762	42.59	3032	34.36		760	42.47	
Middle Taiwan	417	23.31	1975	22.38		418	23.37	
Southern Taiwan	453	25.32	2006	22.73		452	25.27	
Eastern Taiwan	133	7.43	1085	12.29		137	7.66	
Outlets islands	24	1.35	727	8.24		22	1.23	
Urbanization level					<0.001			0.998
1 (highest)	658	36.78	3004	34.04		659	36.83	
2	802	44.83	3262	36.96		800	44.72	
3	111	6.20	1325	15.01		113	6.32	
4 (lowest)	218	12.19	1234	13.99		217	12.13	
Level of care					<0.001			0.998
Hospital center	650	36.33	2897	32.83		650	36.33	
Regional hospital	744	41.59	2983	33.80		745	41.64	
Local hospital	395	22.08	2945	33.37		394	22.03	

P vaues: χ^2/Fisher exact test for categorical variables and t-test for continuous variables.
*Comparison of 'with antidepressants' and 'without antidepressants' (unmatched).
†Comparison of with antidepressants and without antidepressants (one-fold matching).

middle-income countries where access to ultrasound is poor or absent.[39] Moreover, data on preterm births were available disproportionately from high-income countries where monitoring systems are generally more robust and antenatal ultrasound is often used. In addition, the preferred data source was civil registration and vital statistics (CRVS) data, but not all countries have a CRVS system.[40] Furthermore, the definitions of live and preterm births differ among countries (eg, preterm data from Columbia used a preterm birth definition of <38 gestational weeks), contributing to varied

Table 2 Preterm birth factors during different trimesters using Cox regression model

Antidepressants and trimesters	Population	Proportion (%)	Event	PMs	Rate (per 10^3 PMs)	Adjusted HR*	95% CI	P value
Without antidepressants	1789	–	55	16,381.25	3.36	Reference		
With antidepressants	1789	–	87	16,373.60	5.31	1.762	1.351 to 2.294	<0.001
First trimester	1107	61.88	55	10,461.37	5.26	1.650	1.248 to 2.132	<0.001
Ssecond trimester	345	19.28	15	3053.65	4.91	1.431	1.043 to 1.981	0.007
Third trimester	337	18.84	17	2858.57	5.95	2.009	1.675 to 2.587	<0.001

*Adjusted for variables including age, income-related insurance premium, hospital types, urbanization levels, nulliparity or multiparity, multiple gestation, diabetes mellitus, hypertension, dyslipidemia, uteroplacental ischemia or hemorrhage, reproductive tract infection, pre-eclampsia, eclampsia, placenta previa, abruptio placenta, polycystic ovaries, hypogonadism, hypergonadism, pregnancy with history of infertility, morbid obesity or being overweight, and anxiety disorders.
CI, confidence interval; HR, hazard ratio; PM, person-month.

preterm birth rates.[41] Finally, the use of non-population data such as research studies is a limitation. Many low- and middle-income countries have only small or facility-based research studies with limited information available to inform estimation. Therefore, it is hard to decide whether the Taiwanese preterm birth rate is actually lower than the global preterm birth rate.

The overall prevalence rate of preterm birth in pregnant women with depression who were taking antidepressants was not higher than that in the general population, suggesting that other risk factors for preterm birth also existed. That perinatal depression is considered to be the main risk factor leading to non-optimal fatal development and postpartum depression, a condition also related to developmental problems in children, effective treatment for depression during pregnancy is needed.[42 43] Although non-pharmacological interventions are the preferred treatment for mild to moderate depression, antidepressants are still administered for more severe cases or when other treatment options are inaccessible or ineffective.[44] The use of antidepressants occurs in the context of maternal depression.

Up-to-date literature reviews show that large-scale meta-analyses have pointed out that antidepressants are related to the risk of preterm birth,[4 45] but none of these were able to investigate the risk of antidepressant exposure independent of exposure to depression alone. On the other hand, patients who discontinue antidepressants may experience more severe depression symptoms before conception or recurrent depression during pregnancy.[46 47] Therefore, the association between antidepressant treatment and the risk of preterm birth remains uncertain. Deciding whether to start, stop, or switch antidepressants during pregnancy should still be based on the severity of depression and on evaluating risks to both the mother and child.

When stratified by varying types of antidepressants, all such types exposed in pregnant women were associated with an increased risk of preterm birth with a dose–response effect. However, comparisons between specific antidepressants and the risk of preterm birth are still poorly studied. Of the three studies examining TCA exposure, two found an increased risk of preterm delivery.[9 13 48] Both also found that TCA exposure resulted in a greater risk as compared with SSRI exposure.[9 13] In addition, SNRI exposure resulted in an increased risk of preterm birth.[9 12] In our study, TCA, SNRI, and other types of antidepressants resulted in similar risks of preterm birth compared with SSRI exposure, extending the results of previous research. Furthermore, our findings showed that women who had used antidepressants during their third trimester had the highest risk of preterm birth, which

Table 3 Risk of preterm birth stratified by type and dosage of antidepressants

	Population	Event	PMs	Rate (per 10^3 PMs)	Adjusted HR*	95% CI	P value
Without antidepressants	1789	55	16,381.25	3.36	Reference		
With antidepressants	1789	87	16,373.60	5.31	1.762	1.351 to 2.294	<0.001
SSRIs, <1 DDD	52	1	306.60	3.26	1.082	1.003 to 2.401	0.047
SSRIs, ≥1/<2 DDD	134	7	1512.77	4.63	1.537	1.175 to 2.004	<0.001
SSRIs, ≥2 DDD	222	13	2339.87	5.56	1.835	1.418 to 2.398	<0.001
TCAs, <1 DDD	50	2	501.98	3.98	1.321	1.024 to 1.732	0.015
TCAs, ≥1/<2 DDD	114	5	1215.79	4.11	1.363	1.053 to 1.810	<0.001
TCAs, ≥2 DDD	216	13	2305.90	5.64	1.868	1.431 to 2.507	<0.001
SNRIs, <1 DDD	62	2	512.10	3.91	1.295	1.019 to 1.699	0.018
SNRIs, ≥1/<2 DDD	168	6	1482.89	4.05	1.342	1.031 to 1.803	0.003
SNRIs, ≥2 DDD	253	14	2767.80	5.06	1.673	1.287 to 2.188	<0.001
Others, <1 DDD	61	2	459.70	4.35	1.445	1.113 to 1.887	<0.001
Others, ≥1/<2 DDD	198	7	1035.90	6.76	2.239	1.715 to 2.964	<0.001
Others, ≥2 DDD	259	15	1932.31	7.76	2.574	1.930 to 3.385	<0.001

*Adjusted for variables including age, income-related insurance premium, hospital types, urbanization levels, nulliparity or multiparity, multiple gestation, diabetes mellitus, hypertension, dyslipidemia, uteroplacental ischemia or hemorrhage, reproductive tract infection, pre-eclampsia, eclampsia, placenta previa, abruptio placenta, polycystic ovaries, hypogonadism, hypergonadism, pregnancy with history of infertility, morbid obesity or being overweight, and anxiety disorders.
CI, confidence interval; DDD, defined daily dose; HR, hazard ratio; PM, person-month; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

Table 4 Comparison of the risk of preterm birth among women treated with different types of antidepressants

	Population	Event	PMs	Rate (per 10^3 PMs)	Adjusted HR *	95% CI	P value
Total	1789	87	16,373.60	5.31			
SSRIs	408	21	4159.24	5.05	Reference		
TCAs	380	20	4023.67	4.97	0.948	0.640 to 1.233	0.311
SNRIs	483	22	4762.79	4.62	0.816	0.523 to 1.197	0.489
Others	518	24	3427.91	7.00	1.199	0.986 to 1.581	0.062

*Adjusted for variables including age, income-related insurance premium, hospital types, urbanization levels, nulliparity or multiparity, multiple gestation, diabetes mellitus, hypertension, dyslipidemia, uteroplacental ischemia or hemorrhage, reproductive tract infection, pre-eclampsia, eclampsia, placenta previa, abruptio placenta, polycystic ovaries, hypogonadism, hypergonadism, pregnancy with history of infertility, morbid obesity or being overweight, and anxiety disorders.
CI, confidence interval; HR, hazard ratio; PMs, person-months; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

is consistent with the findings of previous longitudinal studies.[49–51]

The mechanisms behind antidepressants and preterm birth remain unclear. However, the increased risk of preterm birth in women with perinatal depression does allow for a few possible explanations. First, maternal stress may increase the risk of preterm birth.[52] Second, antidepressants, mainly SSRIs, pass the placenta barrier, increase the corticotropin-releasing hormone, and result in increased activity within the gestational cortisol system.[53] Moreover, antidepressants alter the 5-HT levels, which can result in the impairment of the placental blood flow; thus, the risk of preterm birth is increased.[54] Women who had filled a prescription for an antidepressant may have also had more severe depression, which places them at a higher risk of preterm birth. Depression in and of itself, rather than the antidepressant medication, might be implicated in the causal pathway of preterm birth.[55] Without treatment for depression, pregnancy-related deaths increase,[56] breastfeeding initiation is lower, maternal and infant bonding is poorer, and infant developmental delays increase.[57] The severity of depression may also explain the observed association between antidepressants and preterm birth, but this was not recorded in the NHIRD. In addition, pregnant women with anxiety may seek regular health assessments and are more likely to be diagnosed with perinatal depression than are those who do not undergo regular assessments. Moreover, depression might be associated with smoking, alcohol consumption, illicit drug use, and poor attendance to obstetric care, all of which contribute to preterm birth.[58–61] Finally, the issue of confounding by indication in the association between antidepressant exposure and the risk of preterm birth should be considered in our study.[62] Without adjusting for indication bias, the indications for prescribing a drug can also be associated with the outcome of interest.[63 64] Therefore, antidepressant exposure may be just an epiphenomenon to other factors associated with depression itself or with depression-related factors, such as age,[65] unhealthy lifestyles,[58–61] socioeconomic inequality,[66] and more severe medical and psychiatric illnesses.[67]

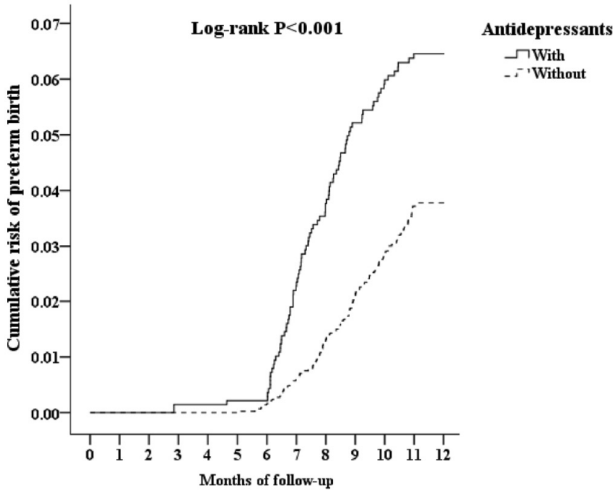

Figure 2 Comparison of the Kaplan-Meier survival analyses for the cumulative incidence risk between the study and control cohorts.

Our study has several strengths. To enhance diagnostic validity, we sought all diagnoses appearing at least twice in outpatient medical records and once in inpatient medical records. In addition, the diagnoses in our study were more reliable than those delivered by proxy, such as via questionnaires and self-reported symptoms.[68] Furthermore, we assessed when and what types of antidepressants were used during pregnancy; these data would have provided information concerning possible heterogeneity in preterm birth risk during the observational period.

Despite the strengths mentioned, our study also has several limitations. First, the NHIRD does not provide complete individual information, such as smoking and alcohol consumption history, unhealthy lifestyle, body mass index and biomarkers, all of which are known to be associated with risk of preterm birth.[69–71] Unhealthy lifestyles and depression are highly interrelated. People with depression with low daily physical activity or heavy drinking patterns are more likely to become depressed over time.[61] Controlling for all unmeasured confounders related to preterm birth was not possible in this study. Moreover, the NHIRD does not allow for assessment of depression severity, which has been found to be a possible risk factor for preterm birth.[33] Women with higher severity of depression may be more likely to receive antidepressants, which may also reflect the higher risk of preterm birth. Therefore, the indication bias could not be fully adjusted.[62] Finally, the DDD did not represent the actual use of antidepressants, and changes in exposure to antidepressants are a complex issue in the Longitudinal Health Insurance Database (LHID). Therefore, we could not precisely estimate the effect of antidepressants on the risk of preterm birth, and future studies are warranted to confirm our findings.

CONCLUSIONS

The use of antidepressants during pregnancy is associated with an elevated risk of preterm birth. All types of antidepressants demonstrated a dose–response effect on preterm birth. However, indication bias in all pharmacoepidemiological studies cannot be completely ruled out. Deciding whether to start, stop, or change antidepressant usage during pregnancy requires an evaluation of the risks associated with treatment against those associated with untreated depression for both the mother and child.

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Correction notice Since Online First publication, the corresponding author's email address has been corrected to lgh@ndmctsgh.edu.tw.

Contributors L-FC drafted the manuscript, developed the concept, and designed the experiments. C-EL and C-HC analyzed and interpreted the data. W-CC and C-HL supervised the manuscript preparation. All authors read and approved the final manuscript.

Funding This study was supported in part by the Tri-Service General Hospital Research Foundation (TSGH-B-110012).

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The Institutional Review Board of Tri-Service General Hospital approved our study protocol (IRB number 2-107-05-009).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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