Lupus women with delivery with higher risk of heart failure compared with those without pregnancy but neutral in major adverse cardiovascular events. A population-based matched cohort study

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Abstract

Objective

Limited data exist regarding the incidence rate and relative risks of major adverse cardiovascular events in women with lupus who have successfully delivered compared to those who have not been pregnant.

Methods

A retrospective, population-based matched cohort study was performed on women with lupus from 2000 to 2006. In total, 149 women with lupus and a successful delivery were enrolled as the study cohort, and 446 women with lupus with no pregnancy, frequency-matched for age, duration of systemic lupus erythematosus, hypertension and diabetes as the comparison cohort. Poisson regression modeling was used to determine the relative risk of a successful delivery on the risk of major adverse cardiovascular events among the women with lupus.

Results

Successful delivery for women with lupus had a neutral effect on major adverse cardiovascular events. The incidence rate of any major adverse cardiovascular event was 1,139 per 100,000 person-years, consisting mainly of heart failure, stroke, and all-cause mortality, with incidence rates of 652, 481 and 481 per 100,000 person-years, respectively. The women with lupus and a successful delivery had a higher incidence rate of heart failure (RR=5.4, 95% CI=1.4–21.7, p<0.017).

Conclusion

Major adverse cardiovascular events and mortality were rare events in the women with lupus of reproductive age. Successful delivery had a neutral effect on major adverse cardiovascular events in the women with lupus, although they had a higher incidence of heart failure.

Key words

lupus, major adverse cardiovascular events, women

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Received on June 18, 2013; accepted in revised form on August 30, 2013.

Funding: this work was supported by grants from the CMRPG39091 from Chang Gung Memorial Hospital, Taiwan; and in part by research grants from the NSC 97-2314-B-075-039.

Competing interests: none declared.

Introduction

Systemic lupus erythematosus (SLE) is a multisystemic autoimmune connective tissue disorder that predominantly affects women of childbearing age. (1, 2) Managing pregnant women with lupus can be challenging. Over the past few decades, improvements in the survival rate and quality of life of lupus patients have led to an increased number of pregnancies during the course of the disease (3).

For women with SLE, being a mother may be one the most challenging roles both psychologically and physically. However, studies focusing on the long-term outcomes of major adverse cardiovascular events (MACE) for this increasing population are lacking. Previous studies (4-7) reporting on the complications in SLE have focused mainly on the period during pregnancy, and long-term follow-up studies (8-10) reporting on the incidence of cardiovascular complications in women with lupus have not evaluated the effect of delivery. Because of the rare occurrence of major adverse cardiovascular events such as myocardial infarction, heart failure, percutaneous coronary intervention, coronary artery bypass graft, stroke, malignant dysrhythmia, thrombolysis therapy, and maternal death in women with lupus, we used a large population-based dataset, the National Health Insurance (NHI) claims records from 2000 to 2010. This is the first study to estimate the incidence and hazard ratios of MACE in lupus women with successful delivery and lupus women without pregnancy.

Methods

Data source

Data for this study were obtained from the Registry of Catastrophic Illness Patients (RCIP), a subset of the National Health Insurance Research Database (NHIRD), Taiwan, from 1997 to 2011. Currently, the NHI programme covers more than 99% of the population of Taiwan. The NHIRD provides medical claims, registration, and reimbursement data, and also inpatient and outpatient registries from all medical facilities contracted with the NHI as well as information regarding all admissions. Patients with SLE were defined as those with three or more outpatient visits within one year, or those who had been hospitalised with a diagnosis of SLE between 2000 and 2010. Diagnostic information in the RCIP is based on the International Classification of Diseases, 9th revision (ICD-9).

All personal identifiers are encrypted by the Bureau of NHI, before release to researchers. Confidentiality assurances were addressed by following the data regulations of the Bureau of NHI, and Institutional Review Board approval (no. 984060B) was waived.

The study cohort

From 2000 to 2006, 3,446 women with SLE were identified. The exclusion criteria were patients who had a first MACE before the diagnosis of SLE, a diagnosis of lupus during pregnancy, pregnancy without successful delivery, MACE before pregnancy, extreme values of maternal age (<10 or >45 years), and those with incomplete or unmatched data (Fig. 1). In total, 149 women successfully gave birth (study cohort), and 446 women were frequency-matched to the study cohort for duration of SLE, age at pregnancy, diabetes and hypertension (comparison cohort) (Table I).

Identification of cases of MACE or death

We examined three types of incident events: MACE, death associated with cardiovascular events, and death from all causes. To identify the timing of the onset of MACE or death, the date of delivery was used as the index date of follow-up. Subjects in the non-pregnant cohort were assigned an index date corresponding to the delivery date of the matched delivery subjects. Each woman was tracked for a new onset of cardiovascular events or death from the index date to the time of the cardiovascular events or death, or until December 31, 2010, whichever came first. The mean follow-up period was seven years.

Major adverse cardiovascular events included any of the following: (1) myocardial infarction (ICD-9-CM codes 410–410.9); (2) heart failure (ICD-9-CM codes 428.0–428.10); (3) percutane-

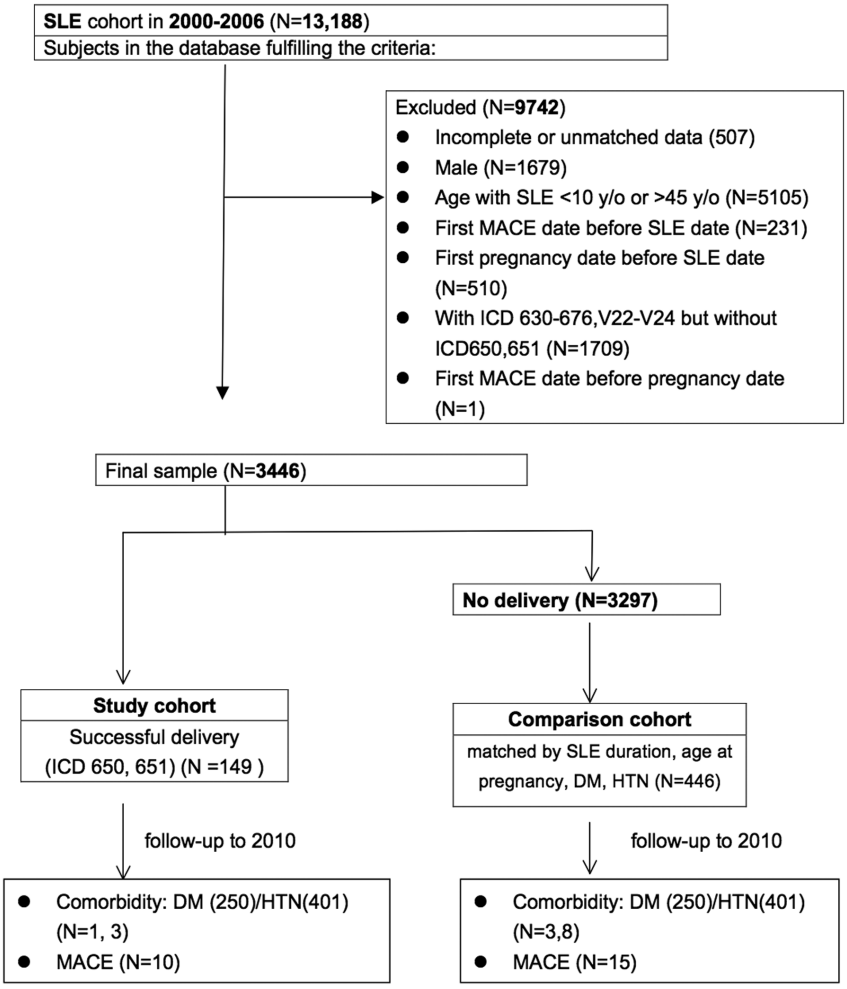

Fig. 1. Patient enrolment flow-chart.
ICD 630: hydatidiform mole, ICD 631: other abnormal product of conception, ICD 632: missed abortion, ICD 633: ectopic pregnancy, ICD 634: spontaneous abortion, ICD 635: legally induced abortion, ICD-636: illegal abortion, ICD 637: unspecific abortion, ICD 638: failed attempted abortion, ICD 639 complication following abortion and ectopic and molar pregnancy, ICD 640: threatened abortion, ICD 641: antepartum haemorrhage abruption placenta, ICD 642: hypertension complicating pregnancy childbirth, ICD 643: excessive vomiting in pregnancy, ICD 644: early or threatened labour, ICD 645 late pregnancy, ICD 646: other complications of pregnancy not elsewhere classified, ICD 647: infectious and parasitic conditions in the mother classifiable elsewhere but complicating pregnancy childbirth or the puerperium, ICD 648: other current conditions in the mother classifiable elsewhere but complicating pregnancy childbirth or the puerperium, ICD 649: other condition or status of the mother complicating pregnancy, childbirth, or the puerperium, ICD 652: malposition and malpresentation of foetus, ICD 653: disproportion in pregnancy labour and delivery, ICD 654: abnormality of organs and soft tissues of pelvis, ICD 655: known or suspected foetal abnormality affecting management of mother, ICD 656: other known or suspected foetal and placental problems affecting management of mother, ICD 657: polyhydramnios, ICD 658: other problems associated with amniotic cavity and membranes, ICD 659: other indications for care or intervention related to labour and delivery not elsewhere classified, ICD 660: obstructed labour, ICD 661: abnormality of forces of labour, ICD 662: long labour, ICD 663: umbilical cord complications during labour and delivery, ICD 664: trauma to perineum and vulva during delivery, ICD 665: other obstructed trauma, ICD 666: postpartum haemorrhage, ICD 667: complications of the administration of anesthetic or other sedation in labour and delivery, ICD 669: other complications of labour and delivery not elsewhere classified, ICD 670: major puerperal infection, ICD 671: venous complications in pregnancy and the puerperium, ICD 672: Pyrexia of unknown origin during the puerperium, ICD 673: Obstetrical pulmonary embolism, ICD 674: Other and unspecified complications of the puerperium, not elsewhere classified, ICD 675: Infections of the breast and nipple associated with childbirth, ICD 676: Retracted nipple associated with childbirth and disorders of lactation, V22: Normal pregnancy, V23: Supervision of high-risk pregnancy, V24: Postpartum care and examination, ICD650: normal delivery, ICD 651: multiple gestation.

ous coronary intervention (ICD-9-CM codes 36.0–36.03 and 36.05–36.09); (4) coronary artery bypass surgery (ICD-9 codes 36.1–36.99 and V45.81); (5) stroke (ICD-9-CM codes 430–437); (6) thrombolysis therapy (ICD-9-CM codes 36.0–36.99); (7) malignant dysrhythmia (ICD-9-CM codes 426.0, 426.12–426.13, 426.51–426.52, 426.54, 427.1, 427.4, 427.41–427.42, and 427.5); and (8) cardiogenic shock (ICD-9-CM code 785.51). Mortality related to MACE was identified using death certificate data files with any diagnosis code, which also indicated the causes of death related to cardiovascular events.

The following ICD-9 codes were not used to define MACE unless they were accompanied with a diagnosis code of cerebral infarction or cerebral haemorrhage: occlusion or stenosis of extracranial arteries without infarction (ICD-9-CM codes 430.00, 431.00, 433.20, 433.30, 433.80, 43.390, 434.90, 434.00, 434.10, and 434.90); basilar, vertebral, and subclavian artery syndrome (ICD-9-CM codes 435.0–435.3); hypertensive encephalopathy (ICD-9-CM code 437.2); cerebral aneurysm, non-ruptured (ICD-9-CM code 437.3); cerebral arteritis (ICD-9-CM code 437.4); and moyamoya disease (ICD-9-CM code 437.5) (11-13).

Statistical analysis

The distribution of cardiovascular events or death was determined based on the person-year method among groups classified by clinical factors. Person-years at risk was used to calculate incidence rates. The association between delivery and MACE and related events adjusting for potential confounders was assessed using Poisson regression models to calculate the relative risk (RR) and their corresponding 95% confidence intervals (CIs). All tests of significance were 2-sided, and a probability value of less than 0.05 was considered significant. All analyses were performed using SAS for Windows version 9.01 (SAS Institute, Cary, NC).

Results

The demographic characteristics and comorbid medical disorders of the study and comparison groups were matched in terms of age at pregnancy, duration of SLE, diabetes and hypertension. A total of 149 patients were identified to have lupus and a successful delivery. The mean age of these patients was 25 years.

The distribution of incident rates of each MACE, cardiovascular event re-

Table I. Baseline characteristics of the study population: Delivery cohort (lupus women with successful deliveries) and Comparison cohort (lupus women who have not delivered, or without successful deliveries).

Variables	Delivery cohort (n=149)	Comparison cohort (n=446)	*p*-value
Delivery age (years)			1
15–19	2	6	
20–24	24	71	
25–29	60	180	
30–34	47	141	
35–39	14	42	
40–44	2	6	
Comorbidity			
Diabetes	1	3	
Hypertension	3	8	

lated death and all-cause death per 100,000 person-years among the groups is shown in Table II. The incidence rate of any MACE was 1,139 per 100,000 person-years, which consisted mainly of heart failure, stroke, and all-cause mortality. Heart failure, stroke and death were the most common MACE among the study group, with incidence rates of 652, 480 and 477 per 100,000 person-years, respectively. No MACE related deaths were documented. The risk of MACE between the groups was not significantly different. However, the study group had a significantly higher risk of heart failure (adjusted RR=5.4, 95% CI=1.4-21.7, $p<0.016$). The numbers of cases of coronary artery bypass surgery, malignant dysrhythmia, cardiac shock, and MACE related death were too small to allow for regression analysis.

Discussion

Most previous studies on SLE complications have focused on the period during pregnancy (4-7). In our study, we focused on the long-term postpartum period. Major adverse cardiovascular events is a widely used concept to evaluate complications in cardiovascular studies (14-15), therefore we used this term to cover these rare but important cardiovascular complications in our study. The aim of the current study was to investigate the effect of a successful delivery on MACE in patients with SLE. We found that the women with SLE and a successful delivery had a higher incidence rate of heart failure compared to those without pregnancy (RR = 5.4, 95% CI = 1.3–21.6, $p<0.017$) but the absolute risk remains very low.

Mortality and stroke in lupus patients

Early work first drew attention to the importance of mortality due to circulatory diseases in patients with SLE, particularly late in the disease course (9). Among the studies published since 1995, the annual mortality rate for non-pregnant lupus patients ranges from 790 to 3,208 deaths per 100,000 person-years (8, 16-19). Similar to these studies, the incidence of mortality in our comparison cohort was 1,080 per 100,000 person-years. In our prior study, we reported the incidence rate of all-cause mortality in lupus patients with a successful delivery to be 428 per 100,000 person-years (13), which is similar to the incidence of mortality in the current study cohort of 480 per 100,000 person-years. The incidence of stroke in SLE has been reported to range from 113 to 553 per 100,000 person-years (10, 13). The incidence of stroke in the study and

Table II. Poisson regression model of potential risk for presence of major adverse cardiac events among systemic lupus erythematosus patients with delivery or not.

		Number of MACE	Number of Total	Incidence	Pr > χ^2	Incidence rate ratio	95% CI	
Myocardial infarction	Comparison cohort	0	446	0.0000				
	Delivery cohort	0	149	0.0000	–	–	–	–
Percutaneous cardiac intervention	Comparison cohort	0	446	0.0000				
	Delivery cohort	0	149	0.0000	–	–	–	–
Coronary artery bypass grafting	Comparison cohort	0	446	0.0000				
	Delivery cohort	0	149	0.0000	–	–	–	–
Heart failure	Comparison cohort	4	446	0.0012				
	Delivery cohort	4	149	0.0065	0.0169	5.4	1.3	21.6
Cerebrovascular accident (stroke)	Comparison cohort	9	446	0.0027				
	Delivery cohort	3	149	0.0048	0.3916	1.7	0.4	6.5
Malignant dysrhythmia	Comparison cohort	0	446	0.0000				
	Delivery cohort	1	149	0.0016	–	–	–	–
Thrombolysis	Comparison cohort	0	446	0.0000				
	Delivery cohort	0	149	0.0000	–	–	–	–
Cardiac shock	Comparison cohort	0	446	0.0000				
	Delivery cohort	0	149	0.0000	–	–	–	–
Death	Comparison cohort	36	446	0.0108				
	Delivery cohort	3	149	0.0048	0.1741	0.4	0.1	1.4
Total MACE	Comparison cohort	43	446	0.0130				
	Delivery cohort	9	149	0.0148	0.7226	1.1	0.5	2.3

Delivery cohort: SLE: women with successful delivery; Comparison cohort : SLE: women without pregnancy; No: number; MACE: major adverse; cardiovascular event; Pr: Poisson regression.

comparison cohorts were 481 and 271 per 100,000 person-years, respectively, which is similar to those reported in prior studies. However, the differences in mortality and stroke were not significantly different between the groups, and a successful delivery seemed to have neutral effect on stroke and mortality.

Heart failure in lupus patients

Patients with SLE may be predisposed to developing CHF as a consequence of ischaemic, hypertensive, or valvular heart disease (20, 21). Women aged 18-44 years with SLE have a more than 2.5-fold increased risk of hospitalization for CHF compared to those without SLE (22). In the current study, the incidence rates of heart failure in the study and comparison cohorts were 652 and 120 per 100,000 person-years, respectively, and the study group had a significantly higher risk (adjusted RR=5.4, 95% CI=1.3-21.6, $p<0.016$). The etiology resulting in CHF among the patients in the present study is not known, however, the increased risk of CHF among the patients with a successful delivery persisted in analysis that included adjustments for the presence of hypertension, diabetes and age. This suggests that factors other than hypertensive heart disease and ischaemic heart disease were contributory.

Limitations

There are several limitations to this study. First, there were a limited number of cases of MACE among the women with lupus, despite the fact that this was a population-based study that covered a 10-year period. Almost all hospitals/clinics are linked to the NHI in Taiwan, and over 99% of the population was covered by the program during the study period. This program makes healthcare easily accessible and affordable for the beneficiaries, however it is possible that we may have missed some cases of MACE who died at home. Second, two important clinical parameters were not available in the NHI claims database, namely clinical/imaging information and the severity of the MACE. Third, the NHI claims data does not include a history of smoking. Thus, we are unable to determine the effect of smoking, even though smoking has been identified as an important risk factor for cardiovascular events (23). Fourth, antiphospholipid syndrome is a known risk factor for cardiovascular diseases in SLE patients, ICD-9 code 286.53 represents antiphospholipid antibody with haemorrhagic disorder in 2011 edition ICD-9. The study period of our NIH dataset was from 2000 to 2010. Therefore, in our study, we could not evaluate the effects of antiphospholipid antibody syndrome on MACE.

Conclusion

Despite such limitations, the NHI claims database provides valuable information for investigating the association between successful delivery and MACE in women with SLE. These events place a large burden on society and the healthcare system, and there should be increased efforts to prevent them. In conclusion, MACE were rare events in women of reproductive age, especially in those with SLE with a successful delivery. Successful delivery for women with lupus had a neutral effect on major adverse cardiovascular events. However, we found that the women with lupus and a successful delivery had a 5.4-fold increased risk of heart failure. Clinicians should therefore be aware of the risk of heart failure in women with lupus who have had a successful delivery.

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