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Fetal–neonatal and maternal pregnancy outcomes in women with rheumatoid arthritis: a population-based cohort study

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ABSTRACT

Objectives Rheumatoid arthritis (RA) may adversely influence pregnancy and lead to adverse birth outcomes. This study estimated the risk of adverse fetal–neonatal and maternal pregnancy outcomes in women with RA.

Design This was a retrospective cohort study.

Setting We used both the National Health Insurance database and the Taiwan Birth Reporting System, between 2004 and 2014.

Participants We identified 2 100 143 singleton pregnancies with 922 RA pregnancies, either live births or stillbirths, delivered by 1 468 318 women.

Outcome measures ORs with 95% CIs for fetal–neonatal and maternal outcomes were compared between pregnancies involving mothers with and without RA using an adjusted generalised estimating equation model.

Results Covariates including age, infant sex, Charlson Comorbidity Index, urbanisation, income, occupation, birth year and maternal nationality were adjusted. Compared with pregnancies in women without RA, pregnancies in women with RA showed that the fetuses/neonates had adjusted ORs (95% CI) of 2.03 (1.66 to 2.50) for low birth weight (n=123), 1.99 (1.64 to 2.40) for prematurity (n=141), 1.77 (1.46 to 2.15) for small for gestational age (n=144) and 1.35 (1.03 to 1.78) for fetal distress (n=60). Pregnancies in women with RA had adjusted ORs (95% CI) of 1.24 (1.00 to 1.52) for antepartum haemorrhage (n=106), 1.32 (1.15 to 1.51) for caesarean delivery (n=398), and 3.33 (1.07 to 10.34) for disseminated intravascular coagulation (n=3), compared with women without RA. Fetuses/neonates born to mothers with RA did not have a higher risk of being stillborn or having fetal abnormalities. Pregnant women with RA did not have increased risks of postpartum death, cardiovascular complications, surgical complications or systemic organ dysfunction.

Conclusions Pregnancies in women with RA were associated with higher risks of multiple adverse fetal–neonatal and maternal outcomes; however, most pregnancies in these women were successful.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study combines data from the National Health Insurance database and the Taiwan Birth Reporting System, between 2004 and 2014, to identify 2 100 143 singleton pregnancies, delivered by 1 468 318 women.
⇒ This study applied a more stringent definition for rheumatoid arthritis (RA) elevated accuracy for RA cases, but at the same time led to a relatively small proportion of RA pregnancies (n=922) among the entire cohort and limited power of study results.
⇒ The study period spanned the emergence of the biologics era; therefore, it is more representative of the patients we currently encounter in practice.
⇒ The National Health Insurance (NHI) database did not hold information on RA disease activity. Information about medication during the study period, though available in the NHI database, was not analysed either. We were therefore unable to evaluate the potential influence of disease activity and medication on maternal and neonatal outcomes.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory autoimmune disease characterised by destructive synovitis. Moreover, RA may affect the internal organs leading to extra-articular injuries and is known to be associated with increased comorbidities.[1] The prevalence of RA ranged from 0.41% to 0.54% among adults in the US population between 2004 and 2014.[2] An epidemiological study conducted in Taiwan revealed that the prevalence of RA was 0.05% between 2001 and 2008; in 2000, the incidence was 17.3 per 100 000 person-years.[3] RA affects women three times more frequently than it affects men.[4] The peak age of onset is during the fourth or fifth decade of life. Yet, RA is not uncommon among younger women; the prevalence of women of childbearing age was up to 0.12% in the UK population.[5]

The management of pregnant women with rheumatic diseases and their children involves rheumatologists, obstetricians and paediatricians. RA may adversely influence pregnancy through several mechanisms, potentially leading to adverse birth outcomes such as low birth weight (LBW),[6] premature birth,[7 8] caesarean section (CS),[7 9] pre-eclampsia, small

for gestational age (SGA) neonates and perinatal death.[7] A population-based study conducted in Taiwan (2001–2003) showed that mothers with RA had increased risks of LBW and SGA babies, pre-eclampsia, and CS compared with unaffected women.[10]

Biologics for treatment of RA were introduced in Taiwan in 2003. Since then, RA disease awareness greatly increased with time, and diseases were diagnosed earlier. By using a more recent cohort in this study, we would like to examine if pregnancy outcomes have changed with the potential shift in certain patient characteristics. In addition, we used dual mechanisms including International Classification of Diseases, Ninth Revision (ICD-9) code and catastrophic illness certificate in classifying RA cases that may identify true patients more accurately, leading to more precise assessment of risks in case versus non-case.

METHODS

Patient and public involvement

Study participants or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Data sources and study design

Data for this retrospective population-based cohort study were obtained from two national databases: (1) the National Health Insurance (NHI) database (established in 1995) and (2) the Taiwan Birth Reporting System (TBRS, established in 1993). All residents are legally required to enrol in the NHI programme, resulting in 99.4% of residents being covered by the end of 2014.[11] In Taiwan, the NHI subsidises essential prenatal care services, including clinical visits, laboratory tests, fetal ultrasound, health education, delivery and infant and postpartum care. The NHI database provides deidentified information regarding patient sex, date of birth, place of residence, insurance details, family relationships, inpatient and outpatient visit dates, medical diagnoses, medical expenditures, prescription details, examinations, operations, procedures and fees incurred. Information on each of the 23 million beneficiaries in the database can be linked through a unique encrypted identifier to other databases, such as the civil registration, death registry, birth registration and other government-held data.[12]

Medical organisations are mandated to submit a birth certificate within 7 days of delivery to facilitate future healthcare for the mother and newborn.[13] The TBRS contains information on all live births and stillbirths (>20 weeks of gestational age or with fetal weight >500 g). During the study period, the TBRS covered more than 99.7% of births registered by the Ministry of Interior in Taiwan.[14 15] The variables collected in the TBRS include demographic, reproductive and socioeconomic characteristics of infants and their parents.

Study cohort

We used the NHI database to identify all pregnancies in Taiwan between 1 January 2004 and 31 December 2014; these data were linked to the TBRS data for the same study period. As multiple births or extreme maternal are known as risk factors to adverse pregnancy outcomes, we excluded multiple births and material age <15 or >45 years from the analysis.[16 17]

In Taiwan, patients with suspected RA are usually referred to rheumatologists for diagnosis and management. Those with a confirmed RA diagnosis are entitled to a medical copayment waiver when they obtain a catastrophic illness certificate.[18] Application for this waiver requires diagnostic information required for RA classification to be submitted to the NHI for expert review. This information includes the patient's clinical records, laboratory data and images. Patients diagnosed with RA ICD-9 code 714.0, and holding a catastrophic illness certificate before the record of pregnancy were assigned to the exposed group (figure 1). The non-exposed groups comprised the remaining pregnant women in the same study period.

Outcome classification

Maternal baseline information (age at pregnancy, nationality, place of residence, income level, occupation and comorbidities) was obtained from the NHI database. Smoking and alcohol consumption were self-reported by the mothers in the TBRS. Infant sex information was also retrieved from the TBRS.

Fetal–neonatal outcomes were obtained from the TBRS. LBW was defined as birth weight <2500 g. SGA (or large) for gestational age (LGA) was defined as birth weight <10th percentile (or >90th percentile) for the gestational age. A birthweight nomogram depicted all live births, recorded in the TBRS, between 2001 and 2012 (online supplemental figure). Premature birth was defined as birth occurring before gestational week 37. Stillbirths were categorised as explained or unexplained.[19] Fetal abnormalities were compared with inpatient claims data from the NHI database using the ICD-9 codes 655 (known or suspected fetal abnormality affecting management of mother), or by presence of any congenital defect codes according to TBRS. Diagnostic information regarding fetal distress was retrieved from the NHI database with ICD-9 codes 656.3x and 659.7x. All codes used to identify fetal–neonatal and maternal outcomes are listed in online supplemental table 1.

Maternal outcome measures were collected during pregnancy until the end of delivery-related hospitalisation (figure 1). The outcomes included death, cardiovascular events, events and procedures during delivery, events and complications during surgery and others.[20] Maternal deaths were further as certained using the Taiwan National Death Registry, which records the causes of death for all deceased citizens. CS information was retrieved from the TBRS. All other outcomes were

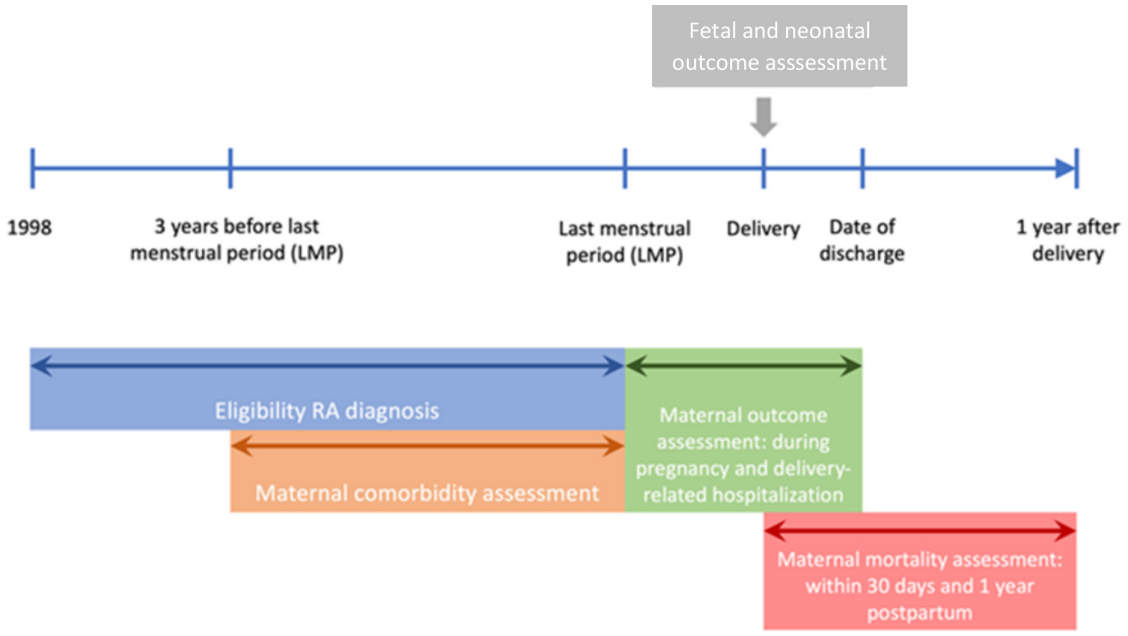

Figure 1 Study diagram.

identified using the ICD-9 codes from the NHI database (online supplemental table 1).

Covariate definitions

We identified maternal confounders (maternal age, level of urbanisation, income level, occupation and nationality) and fetal/neonatal confounders (birth year and infant sex) as covariates. Each individual's place of residence was assigned to one of the 369 towns or districts in Taiwan. The level of urbanisation for these 369 towns or districts was designated as urban, suburban or rural.[21] Occupations were classified into five categories: (1) civil servants, teachers and military personnel/veterans; (2) professionals and non-manual workers; (3) manual workers; (4) other and (5) dependents. Income levels were estimated using the payroll of the employees and the business income of employers.

We assessed maternal comorbidities using the validated Charlson Comorbidity Index (CCI) for ICD-9 codes.[22] We identified 17 categories of CCI comorbidities: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatological disease, peptic ulcer disease, mild liver disease, diabetes mellitus (DM), DM with chronic complications, hemiplegia or paraplegia, renal diseases, any malignancy (including leukaemia and lymphoma), moderate to severe liver disease, metastatic solid tumour and AIDS. Each category was assigned a weighted score, and the sum was calculated for each subject. The rheumatological disease category was excluded from the CCI calculation, in this study. Maternal age was treated as continuous covariate, whereas the other covariates were treated as categorical.

Statistical analysis

The incidence of each outcome was compared between the exposed and non-exposed groups. We used the generalised estimating equation model to estimate the OR, considering that a woman could have had consecutive pregnancies during the study period.[23] Both crude and adjusted ORs are reported with 95% CIs. The correlation structure was built based on an autoregressive model. The model was adjusted for factors mentioned in the covariate definitions section. As entry to TBRS is reinforced by law, the rates of missing data are essentially low, all analyses were performed on complete data. Hence, adjustment for missing data handling was not applied. Smoking and alcohol consumption collected in TBRS were self-reported, which may lead to a high likelihood of under-reporting. These two lifestyle factors were thus not included as covariates for adjustment due to the unreliability. A two-sided test with a 5% level of significance was used for all hypotheses. All analyses were performed using SAS V.9.4 (SAS Institut).

RESULTS

Baseline characteristics

The demographic, maternal and infant characteristics in the exposed and non-exposed groups are summarised in table 1. Between 2004 and 2014, there were 2 100 143 singleton pregnancies, involving either live births or stillbirths, delivered by 1 468 318 women; 922 pregnancies (0.044%) involved women with RA.

Pregnant women with RA were older (mean, 32.4 years) than those without RA (30.2 years) at the time of pregnancy. Pregnant women in the exposed group were more commonly employed, had higher incomes and were engaged in non-manual work. More than 13% of the

Table 1 Baseline characteristics of pregnant women with or without rheumatoid arthritis

	With RA (n=922)		Without RA (n=2,099,221)		P value
Age at pregnancy, years, mean (SD)	32.43 (4.42)		30.18 (4.75)		<0.0001
<25	49	(5.31)	293460	(13.98)	
25–34	594	(64.43)	1466672	(69.87)	
>34	279	(30.26)	339089	(16.15)	
Male infants, n (%)	476	(51.63)	1093673	(52.10)	0.7742
Foreign nationals, n (%)	18	(1.95)	177071	(8.44)	<0.0001
Place of residence, n (%)					0.2362
Urban	597	(64.75)	1319524	(62.86)	
Suburban	266	(28.85)	632788	(30.14)	
Rural	58	(6.29)	134045	(6.39)	
Unknown	–*		12864	(0.61)	
Income levels, n (%)					<0.0001
Quintile 1	163	(17.68)	425804	(20.28)	
Quintile 2	168	(18.22)	472937	(22.53)	
Quintile 3	156	(16.92)	365267	(17.40)	
Quintile 4	213	(23.10)	428999	(20.44)	
Quintile 5	222	(24.08)	406043	(19.34)	
Unknown	0	0.00	171	(0.01)	
Occupation, n (%)					<0.0001
Dependents	189	(20.50)	550723	(26.23)	
Civil servants, teachers, military personnel and veterans	72	(7.81)	105345	(5.02)	
Non-manual workers and professionals	396	(42.95)	832357	(39.65)	
Manual workers	161	(17.46)	353248	(16.83)	
Other	104	(11.28)	257548	(12.27)	
Charlson comorbidity index†, mean (SD)	0.17 (0.54)		0.03 (0.23)		<0.0001
0, n (%)	800	(86.77)	2044417	(97.39)	
1, n (%)	105	(11.39)	46420	(2.21)	
≥2, n (%)	17	(1.84)	8384	(0.40)	
Smoking, n (%)	–*		1829	(0.09)	0.8326
Alcohol consumption, n (%)	0	0.00	302	(0.01)	0.6065

*Numbers <3 are not displayed, per the confidentiality policies of the NHI database.
†Rheumatological disease category was excluded for calculation.
NHI, National Health Insurance; RA, rheumatoid arthritis.

pregnant women with RA had one or more comorbidities at baseline. The average CCI score was significantly higher in pregnant women with RA (0.17) than in those without (0.03, p<0.0001). No differences in the rates of smoking or alcohol consumption during pregnancy, place of residence or male infant sex were found between the two groups.

Fetal–neonatal outcomes

The fetal–neonatal outcomes of the two groups are compared in table 2. In the crude analysis, infants born to mothers with RA more commonly demonstrated stillbirth when analysed separately by explained and unexplained categories, LBW, prematurity, SGA, 1 min Apgar score <7, fetal distress and any type of fetal abnormality. After adjusting for predefined covariates, higher risks for LBW, prematurity, SGA, 1 min Apgar score <7, and fetal distress were observed among infants in the exposed group (table 2).

The difference between explained and unexplained stillbirths alone and fetal abnormalities became insignificant after adjustments. Only 13 (1.41%) stillbirths were identified among the 922 pregnant women with RA. The risks for total stillbirths, LGA and 5 min Apgar score <7 were not significantly different between the groups, before and after regression analysis.

Maternal outcomes

Maternal outcomes are presented in table 3. Pregnant women with RA experienced antepartum haemorrhage (APH) and required CS more often than those without RA, after adjusting for covariates. A small (three events

Table 2 Fetal–neonatal outcomes in pregnant women with and without rheumatoid arthritis

	No of events (%)							
	With RA (n=922)		Without RA (n=2 099 221)		Crude OR (95% CI)		Adjusted OR (95% CI)*	
Stillbirth	13	(1.41)	16225	(0.77)	1.39	(0.20 to 9.84)	1.55	(0.89 to 2.68)
Explained stillbirth	†-		1639	(0.08)	1.89	(1.07 to 3.34)‡	1.16	(0.16 to 8.30)
Unexplained stillbirth	12	(1.30)	14586	(0.69)	1.84	(1.07 to 3.18)‡	1.59	(0.90 to 2.82)
Low birth weight (<2500 g)	123	(13.34)	138742	(6.61)	2.17	(1.77 to 2.65)‡	2.03	(1.66 to 2.50)‡
Prematurity (<37 weeks)	141	(15.29)	159997	(7.62)	2.21	(1.83 to 2.67)‡	1.99	(1.64 to 2.40)‡
Small for gestational age	144	(15.62)	206079	(9.82)	1.66	(1.37 to 2.01)‡	1.77	(1.46 to 2.15)‡
Large for gestational age	68	(7.38)	206308	(9.83)	0.75	(0.58 to 0.96)	0.66	(0.51 to 0.84)
Apgar score at 1 min (<7)§	30	(3.25)	40361	(1.92)	1.73	(1.19 to 2.51)‡	1.54	(1.05 to 2.25)‡
Apgar score at 5 min (<7)§	†-		8275	(0.39)	0.28	(0.04 to 1.98)	0.24	(0.03 to 1.71)
Fetal distress	60	(6.51)	103035	(4.91)	1.36	(1.04 to 1.79)‡	1.35	(1.03 to 1.78)‡
Fetal abnormalities, any	65	(7.05)	118691	(5.65)	1.3	(1.01 to 1.67)‡	1.16	(0.90 to 1.49)

*Adjusted for age, infant sex, Charlson comorbidity index, urbanization, income, occupation, birth year, and maternal nationality
†Numbers <3 is not displayed, as per the confidentiality policies of the NHI Database
‡p<0.05.
§Apgar score of live birth
.NHI, National Health Insurance; RA, rheumatoid arthritis.

out of 922 pregnancies, 0.33%) but elevated rate for disseminated intravascular coagulation (DIC) was found among women with RA, leading to an adjusted OR 3.33. However, there were no deaths within 30 postpartum days among the women with RA, and fewer than three deaths within one postpartum year (the absolute number is not displayed, per the NHI database's confidentiality policy). The regression model did not associate RA with increased risks for hypertensive disorders, gestational diabetes or other major complications during pregnancy and the immediate postpartum period.

DISCUSSION

Our study reveals that neonates born to mothers with RA had a twofold increase in the risk for LBW and prematurity and were 1.7 times more likely to be SGA. They also had a 50% higher risk of having Apgar scores of <7 at 1 min and a 35% increased risk for fetal distress. More mothers with RA experienced APH and CS compared with those without RA. Although there were three times more likely to experience DIC, the absolute number of DIC cases was few in the RA cohort and no DIC-related deaths occurred. We did not find a higher risk for stillbirths or fetal abnormalities among pregnancies in women with RA. Pregnancies in women with RA are associated with more fetal/neonatal and material adverse outcomes at peripartum period, but they did not translate into detrimental consequences of the mothers and the neonates in the immediate post-partum follow-up.

Several previous studies have investigated a relationship between RA and pregnancy outcomes.[2 6–10 24–28] The rapid progress in immunology and clinical research during the past two decades has led to early diagnoses, more aggressive interventions and tight disease control for expectant mothers with RA. Our study period spanned the emergence of the biologics era and the evolution of diagnostic and treatment strategies. Hence, this cohort is more representative of the patients we currently encounter in practice.

Mothers with RA are more likely to give birth to LBW and SGA babies in our study. These observations are consistent with those of most previous studies that have examined different ethnic populations and time periods.[2 6–8 10 24–26 28] The differences between the RA and reference groups remained significant after adjusting for infant sex, maternal age, socioeconomic factors and maternal comorbidities. While some researchers have suggested that these phenomena are mediated by disease activity or the use of prednisolone,[6 24] we did not look at these associations in this study. Similarly, our observation of an increased risk for premature deliveries among mothers with RA has been repeatedly observed.[2 7–9 24 26–28] Lin *et al* conducted a population-based study using 2001–2003 NHI database to examine the relationship between RA and adverse pregnancy outcomes.[10] The study used ICD9-CM code 714.0 to identify RA cases, while our study use dual criteria by adding catastrophic illness certificate as another filter, causing smaller but more perhaps more precise cohort of interest. Despite complete separation of study period and narrowing of exposure cohort selection, LBW, SGA and CS have been consistently observed at higher frequencies in pregnancies in RA women. A twofold increased risk for pre-eclampsia was found in RA women by Lin *et al*, but not in our cohort. On the contrary, we noticed nearly twice increase in preterm delivery. In fact, the rates of preterm birth and LBW are 1.8 and 1.6 times greater than reported by Lin *et al*. As mentioned previously, we did not assess whether such differences

Table 3 Maternal outcomes in pregnant women with and without rheumatoid arthritis

	No of events (%)							
	With RA (n=922)		Without RA (n=2 099 221)		Crude OR (95% CI)		Adjusted OR (95% CI)†	
Death								
Death ≤30 days post partum	0	0.00	281	(0.01)	N/A		N/A	
Death ≤1 year post partum	-‡		682	(0.03)	3.35	(0.47 to 23.82)	2.35	(0.32 to 17.17)
Cardiovascular events								
Acute myocardial infarction	0	0.00	106	(0.01)	N/A		N/A	
Shock	0	0.00	1284	(0.06)	N/A		N/A	
Arrhythmias requiring cardioversion	-‡		708	(0.03)	3.38	(0.48 to 23.88)	2.61	(0.37 to 18.56)
Pregnancy-related hypertension	34	(3.69)	54 806	(2.61)	1.45	(1.02 to 2.07)*	1.14	(0.79 to 1.63)
Pre-eclampsia	26	(2.82)	36 792	(1.75)	1.66	(1.10 to 2.50)*	1.30	(0.85 to 1.97)
Eclampsia	0	0.00	1533	(0.07)	N/A		N/A	
Puerperal cerebrovascular diseases	-‡		1799	(0.09)	1.20	(0.17 to 8.43)	0.80	(0.11 to 5.76)
Thromboembolism	0	0.00	233	(0.01)	N/A		N/A	
Events and procedures during delivery								
Amniotic fluid embolism	0	0.00	227	(0.01)	N/A		N/A	
Antepartum haemorrhage	106	(11.50)	188 113	(8.96)	1.33	(1.08 to 1.64)*	1.24	(1.00 to 1.52)*
Severe postpartum haemorrhage	35	(3.80)	58 395	(2.78)	1.42	(1.01 to 1.99)*	1.37	(0.98 to 1.93)
Premature rupture of membranes	0	0.00	84	0.00	N/A		N/A	
Chorioamnionitis	6	(0.65)	8075	(0.38)	1.68	(0.76 to 3.74)	1.54	(0.69 to 3.43)
Caesarean delivery	398	(43.17)	705 109	(33.59)	1.57	(1.37 to 1.80)*	1.32	(1.15 to 1.51)*
Events and procedures during surgery								
Severe anaesthesia complications	0	0.00	230	(0.01)	N/A		N/A	
Thorax, abdomen and pelvis injuries	-‡		896	(0.04)	2.64	(0.37 to 18.68)	2.46	(0.35 to 17.47)
Intracranial injuries	4	(0.43)	4937	(0.24)	1.88	(0.71 to 5.00)	1.73	(0.64 to 4.69)
Blood transfusion	10	(1.08)	13 342	(0.64)	1.70	(0.90 to 3.19)	1.41	(0.75 to 2.65)
Hysterectomy	0	0.00	1700	(0.08)	N/A		N/A	
Operations on heart and pericardium	-‡		2140	(0.10)	1.02	(0.14 to 7.17)	0.78	(0.11 to 5.49)
Others								
Acute renal failure	0	0.00	532	(0.03)	N/A		N/A	
Adult respiratory distress syndrome	-‡		1336	(0.06)	1.75	(0.25 to 12.39)	1.28	(0.18 to 9.24)
Sepsis	7	(0.76)	7002	(0.33)	2.34	(1.11 to 4.91)	1.95	(0.92 to 4.13)
Disseminated intravascular coagulation	3	(0.33)	1658	(0.08)	4.15	(1.34 to 12.88)*	3.33	(1.07 to 10.34)*
Pulmonary oedema	-‡		330	(0.02)	6.44	(0.91 to 45.60)	4.03	(0.54 to 29.83)
Mechanical ventilation	19	(2.06)	26 174	(1.25)	1.67	(1.02 to 2.74)*	1.35	(0.82 to 2.23)
Gestational diabetes	67	(7.27)	13,3028	(6.34)	1.17	(0.91 to 1.51)	0.92	(0.71 to 1.19)

*p<0.05.
†Adjusted for age, infant sex, Charlson Comorbidity Index, urbanisation, income, occupation, birth year and maternal nationality.
‡Numbers <3 are not displayed, as per the confidentiality policies of the National Health Insurance database.
.N/A, not applicable; RA, rheumatoid arthritis.

have association with disease activity or medication use in different time periods.

A low Apgar score at 1 min and fetal distress were more common in neonates born to mothers with RA. However, a recent policy statement published by the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists suggests that had low 1 min Apgar score, alone, does not predict an infant's outcome.[29] The absolute risk differences for low 1 min Apgar scores and fetal distress between the two groups were small (1.33% and 1.6%, respectively). Moreover, there were only a few cases (less than 3) that had an Apgar score <7 at 5 min, indicating that even the small subset of newborns that demonstrated low 1 min Apgar scores demonstrated rapid improvement in their physiological circulatory, respiratory or central nervous functions. This suggests that most live neonates born to mothers with RA did not experience clinically significant perinatal asphyxia or hypoxia.

Infants born to mothers with RA has higher risk of fetal abnormality (7.05% in the RA pregnancies, 5.65% in the non-RA pregnancies) before adjusting for predefined covariates. This finding is higher than the estimated incidence of malformations of 2%–3% in a general

population.[30] The definition of fetal abnormalities in our study consists of two conditions: (1) ICD-9 code 655 (known or suspected fetal abnormality affecting management of the mother) found peripartum inpatient service or (2) presence of congenital anomalies according to coding by TBRS. It is possible that using the ICD-9 code 655, events that were not fetal malformation or congenital defects were reported, causing a high rate of fetal abnormalities in both RA and non-RA pregnancies.

Certain haemorrhagic or coagulative abnormalities were observed in the current study. We identified a 24% increase in APH risk among pregnant women with RA. Defined as bleeding from the genital tract during the second half of pregnancy,[31] the reported incidence of APH is around 3.5% and varies with age, parity and social status.[32] The incidence of APH in both the RA (11.5%) and the reference group (8.96%) in this study seemed to be higher than that seen in the historical data. The clinical implication of the elevated incidence of APH in both groups is unclear. Certain pregnancy adverse events reported having associations with APH were elevated in the RA group in our study, like premature delivery and CS in the RA group. However, these events did not lead to associated detrimental outcomes, such as maternal mortality, massive bleeding requiring blood transfusion, hysterectomy or stillbirths. In addition, we identified three DIC cases among the patients in the RA group, yielding threefold higher odds of DIC in this group than in the reference group. Acute obstetrical bleeding is thought to be a leading cause for DIC.[33] The increased risk of APH in our RA group may partly explain this phenomenon. While systemic inflammatory disorders like RA are well known as risk factors for hypercoagulable states, DIC has not been identified as an associated complication of RA. The rate of DIC was 0.33% and 0.08% for the RA group and the reference group, respectively. These rates are within the range of reported rates of DIC during pregnancy among cohorts (0.03%–0.35%).[34 35] With very few events, we cannot exclude the increased OR was a chance finding. Finally, although obstetrical DIC has been associated with a series of potentially life-threatening conditions,[33] we did not observe this phenomenon in our study.

Forty-three per cent of pregnant women with RA underwent CS. Other studies almost uniformly reported a higher CS rate in pregnant women with RA.[2 6 7 9 10 24–28] Owing to the restrictions of the NHI database, we could not distinguish cases of elective CS from emergent ones, nor could we ascertain the reason for choosing caesarean delivery. More evidence is needed to provide an in-depth understanding of the risk of CS in pregnant women with RA.

Previous studies have shown conflicting results regarding pregnancy-related hypertension and pre-eclampsia/eclampsia in pregnant women with RA. Whereas some found a positive correlation with these complications in pregnant women with RA,[10 24 26 28] others did not.[2 8 9 26] Our study showed a relatively low prevalence of pre-eclampsia (2.82%) in pregnant women with RA, and the risk was no longer detectable after adjusting for covariates. Overall, pregnant women with RA had more significant comorbidities, the general obstetric population requires management of chronic hypertension.

A few limitations of this study require discussion. First, we did not analyse medication use during the study period. Thus, we were unable to evaluate the potential influence of medication on maternal and neonatal outcomes. Second, information about RA disease activity and laboratory data was lacking in National Health Insurance Research Database (NHIRD). Several study groups had observed increased risks for negative pregnancy outcomes, including LBW, SGA and preterm birth, with higher disease activity and/or elevated inflammatory markers in women with RA or juvenile idiopathic arthritis.[6 36 37] Without disease activity information, we could not assess whether some of our observations can be explained by this important factor. Third, we did not conduct long-term follow-up for the mothers or newborns. We were unable to assess whether any of our findings had a clinically significant influence on long-term maternal health or child development. Fourth, the potential for misclassification cannot be entirely excluded during claims database research. This may cause overestimation or underestimation of certain outcomes (such as a higher rate of APH in both the RA and non-RA groups) or categorise study subjects erroneously to the exposure versus non-exposure cohorts. However, using more stringent RA case definition can partly lessen the later risk. Lastly, there were several maternal outcomes observed with low event number (less than 5) in the RA group, made risk estimates imprecise. One should interpret the results cautiously to avoid excessive attribution.

In summary, pregnancies among women with RA are associated with higher relative risks for various adverse maternal and fetal outcomes. However, the absolute risks of maternal death and stillbirth remain low; most pregnancy-related complications can be corrected with proper care by a multi-disciplinary team. These results are reassuring to both patients with RA and their healthcare providers.

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Patient consent for publication Not applicable.

Ethics approval This study was approved by the Chang Gung Memorial Hospital Institutional Review Board (202 001 442B0). This study was exempted from the requirement for patient consent because it analysed anonymised secondary data.

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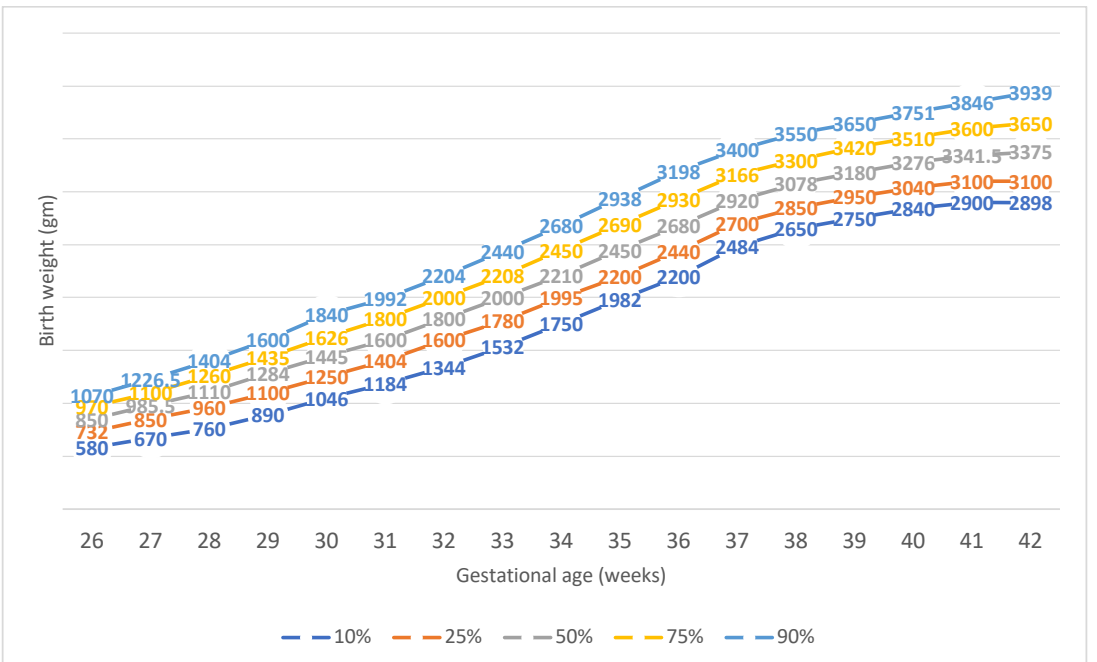
Supplementary Figure 1. Nomogram for birth weight summarized from the Taiwan National Birth Registry (2001-2012)



Supplementary Table 1. Disease definitions

Disease definition	
Delivery	DRG code: 0371A, 0371a, 0373B, 0373b, 0373A, 0373a, 0373C, 0373c ICD-9 CM code: V27, 650, 651, 652 ICD-op-code: 72, 73, 74
Cardiovascular complications	
Acute myocardial	410.xx
Aneurysm	441.xx
Cardiac arrest/ ventricular fibrillation	427.41, 427.42, 427.5
Heart failure	669.4x, 997.1
Shock	669.1x, 785.5x
Conversion of cardiac rhythm	99.6x
Pregnancy-related hypertension	642.3x 642.9x 642.4x 642.5x 642.6x 642.7x
Preeclampsia	642.4x 642.5x 642.6x 642.7x
Eclampsia	642.6x
Gestational hypertension	642.3x 642.9x
Puerperal cerebrovascular disorders	430, 431, 432.x, 433.xx, 434.xx, 436, 437.x, 671.5x, 674.0x, 997.2, 999.2
Thrombotic embolism	415.1x, 673.0x, 673.2x, 673.3x, 673.8x,
Events and procedures during delivery	
Amniotic fluid embolism	673.1x

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Antepartum hemorrhage	641.1x 641.2x 641.3x 641.8x 641.9x
Postpartum hemorrhage due to atony	666.1x
Postpartum hemorrhage not due to atony	666.0x 666.2x 666.3x
Severe postpartum hemorrhage	[666.0x-666.3x] plus either blood transfusion [99.0x] or hysterectomy [68.3x-68.9]
Premature rupture of membranes	658.1x
Chorioamnionitis	658.4x
Cesarean delivery	Birth Registration
Events and procedures during surgery	
Severe anesthesia complications	668.0x, 668.1x, 668.2x
Thorax, abdomen, and pelvis injuries	860.xx-869.xx
Intracranial injuries	800.xx, 801.xx, 803.xx, 804.xx, 851.xx, 854.xx
Blood transfusion	99.0x
Hysterectomy	68.3x-68.9
Operations on heart and pericardium	35.xx, 36.xx, 37.xx, 39.xx
Other	
Acute renal failure	584.x, 669.3x
Adult respiratory distress syndrome	518.5, 518.81, 518.82, 518.84, 799.1
Sepsis	038.xx, 995.91, 995.92
Disseminated intravascular coagulation	286.6, 286.9, 666.3x
pulmonary edema	428.1, 518.4
Temporary tracheostomy	31.1

Ventilation	93.90, 96.01-96.05, 96.7x
Gestational diabetes	648.8x
Low birth weight	Birth Registration, <2500 g
Preterm maturity	Birth Registration, <37 week
Fetal distress	656.3x, 659.7x
Fetal abnormalities, any	Birth Registration + inpatient claim data (ICD-9 (655.xx))
Central nervous system malformations	655.0x
Chromosomal abnormalities	655.1x
Hereditary disease in family possible affecting fetus	655.2
Suspected damage due to viral or other diseases in the mother	655.3x 655.4x
Suspected damage due to drugs or radiation	655.5x 655.6x
Decreased fetal movements	655.7x
Other/unspecified abnormalities	655.8x 655.9x
Stillbirth	Birth Registration

Abbreviations: DRG, Diagnosis Related Groups; ICD, International Classification of Diseases