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ORIGINAL ARTICLE

Comparison of pregnancy outcomes between indigenous and non-indigenous lupus patients

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Key words
pregnancy, live birth, adverse outcomes, indigenous, lupus.

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Abstract

Aim: To compare pregnancy outcomes between IA and non IA lupus patients.
Background: Pregnancy in lupus patients confers an increased risk of maternal and fetal morbidity. There are no data on pregnancy outcomes for indigenous Australian (IA) patients with lupus.
Methods: Using state-wide longitudinal hospital morbidity data, we studied 702 pregnancies in IA ($n = 31$) and non-indigenous (NI) patients with lupus ($n = 357$) in Western Australia and compared rates for live birth (LB), preterm birth (PB) and gestational complications in the period 1985–2015. Results are presented as medians or frequency.
Results: IA patients had proportionally more pre-existing renal disease (35 vs 13%, $P < 0.01$) and lower socio-economic status ($P = 0.02$). Age at first pregnancy was lower in IA patients (27 vs 30 years, $P < 0.001$), recorded gravidity was similar (2 vs 2, $P > 0.6$) and elective termination ($n = 138$) was more frequent in NI than IA pregnancies (21.1 vs 4.8%, $P < 0.01$). For continued pregnancies (59 in IA and 505 in NI), respective outcomes were as follows: LB 84.7% versus 91.5% ($P = 0.15$), spontaneous abortion 13.5% versus 6.9% ($P = 0.13$), (pre-)eclampsia 8% versus 9.9% ($P = 0.89$), PB 12% versus 13.4% ($P = 0.98$) and caesarean delivery 30% versus 47.2% ($P = 0.02$). Gestational diabetes (26% vs 6.1%), renal flares (20% vs 5.6%) and infections (22% vs 6.3%) were all more frequent in IA lupus pregnancies (all $P < 0.001$).
Conclusions: The burden of comorbidities was higher in IA patients with lupus due to renal flares, gestational DM and infections. Although PB rates were overall high, they were, however, similar for IA and NI lupus pregnancies, as were LB rates.

Introduction

Adverse maternal and fetal pregnancy outcomes (APO) are common among females with systemic lupus erythematosus (SLE, hereafter 'lupus'), with up to 25% of lupus pregnancies reported ending with an abortive outcome, whereas 40% of births are preterm delivery (PB) or small for age babies.[1,2] Maternal morbidity is an important contributor to APO,[3,4] where racial disparities have been documented with worse pregnancy outcomes in black patients with lupus.[5–7] In Australia, indigenous Australians (IA) make up 3.8% of the Australian population, are overrepresented in lupus cohorts and have more lupus complications, including worse renal outcomes and survival than non-indigenous (NI) patients.[8–10] Despite some improvements in maternal health, preterm and stillbirth (SB) rates in IA overall remain higher than in NI counterparts.[11,12] Against this background, IA patients with lupus are at greater risk of APO than NI patients with lupus, but data on pregnancy in IA patients with lupus are lacking. We compared fetal outcomes and maternal morbidity across 702 pregnancies for IA and NI patients with lupus.

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Conflict of interest: None.

Methods

Data were sourced from the Western Australia Rheumatic Disease Epidemiological Registry (WARDER)

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that contains routinely collected health data for patients with rheumatic diseases from public and private healthcare organisations in Western Australia and has been applied in earlier studies.[10,13,14] WARDER participants hospitalised with SLE were identified by ICD-9-CM: 695.4 and 710.0, and ICD-10- AM: M32.0, M32.1, M32.8, M32.9, L93.0, L93.1 and L93.2 between 1 January 1985 and 31 December 2014. A diagnostic code for SLE in hospital discharge data has an 80–96% positive predictive value to correctly identify patients fulfilling SLE classification criteria, whereas 94% of patients with SLE are hospitalised at least once during their disease course.[15,16] This implies we have captured the majority of SLE patients in WA during the 30-year study period in our database. The final data set for this study contained sociodemographic data, all principal and secondary diagnoses and procedure codes for hospital episodes before and after the index SLE event. We recorded the following pregnancy data: live births (LBs), fetal outcomes including spontaneous and induced abortion, SB, PB and maternal comorbidities (renal flares, infections and gestational diabetes) and lifestyle factors (smoking, harmful alcohol use and obesity) in the Hospital Morbidity Data Collection (HMDC). These were all identified by previously validated diagnostic and procedural codes (Supplemental Table 1), with renal flares captured defined using a previously published ICD coding algorithm to capture glomerulonephritis (proteinuria with/without haematuria)[10,15] in the absence of gestational proteinuria or eclampsia. Infections were defined as pneumonia, sepsis or bacteraemia, urinary tract infection or skin and soft tissue infections as described earlier.[14] IAs are registered in HMDC according to self-identification during any hospital contact. Socioeconomic status was based on census-based time-averaged scores for Index of Relative Socio-Economic Advantage and Disadvantage (IRSAD) and divided into quintiles (quintile 1 – most disadvantaged through to quintile 5 – most advantaged). The Western Australia Department of Health Ethics Committee provided approval for this project (project no. 2016.24). Results presented are median with interquartile range (IQR), frequency and proportion and odds ratios (ORs) with 95% confidence intervals (CIs). Differences between groups were analysed with Mann–Whitney U test and chi-squared test with Fisher's exact test for small numbers. Two-tailed P values <0.05 indicated statistical significance.

Results

There were 702 registered pregnancies among 31 IA and 357 NI patients with lupus. IA patients were younger at lupus diagnosis (21 years vs 28 years, $P < 0.01$) and at first pregnancy (27 years vs 30 years, $P = 0.02$) and were more frequently socially disadvantaged (19.4% vs 6.2%, $P = 0.02$), although gravidity (median 2) was similar in both groups. During a median observation time of 43 months (IQR: 20–105) before the first pregnancy, IA patients had accumulated a higher burden of LN (35.5% vs 13.2%, $P < 0.01$) and pre-existing comorbid conditions, including DM and tobacco use (Table 1).

A total of 138 pregnancies (19.8%) were terminated (Table 2), with an overall higher proportion of pregnancies terminated in NI than IA patients with lupus (21.1% vs 4.8%, $P < 0.01$), although this difference decreased over time (Supplemental Fig. 1A). The proportion of LB in continued lupus pregnancies was 91.6% (517/564) overall with a non-significant difference observed between IA (50/59, 84.7%) and NI (462/505, 91.5%) pregnancies (OR: 0.52, 95% CI: 0.24–1.19) ($P = 0.15$) (Table 2). The proportion of LB with PB (12.1% overall) was similar for both groups (OR: 0.86, 95% CI: 0.32–2.01, $P = 0.98$), whereas IA patients were significantly less likely to have a delivery by caesarean (OR: 0.47, 95% CI: 0.24–0.87, $P = 0.02$). The proportion of pregnancies ending in spontaneous abortion (overall 7.6%) was higher for IA pregnancies (13.5% vs 6.9%), but the difference was not statistically significant (OR: 1.91, 95% CI: 0.79–4.10, $P = 0.13$). SB rates (1.7% overall) were alike in both IA and NI pregnancies. There was slight but non-significant increase over the study period in the proportion of pregnancies ending in pregnancy loss (spontaneous abortion and SB) in IA patients (Supplemental Fig. 1B). Maternal complications were more frequent in IA than NI patients with lupus, with significantly higher odds in IA patients observed for gestational DM (OR: 5.27, 95% CI: 2.46–70.97, $P < 0.001$), infections (4.09,

Table 1 Baseline characteristics of pregnant patients with systemic lupus erythematosus by cultural background

Patients	IA ($n = 31$)	NI ($n = 356$)	P value
Age lupus onset (years)	21 (19–26)	28 (27–29)	<0.01
Age first pregnancy	27 (22–32)	30 (29–31)	0.02
Gravidity	2 (2–4)	2 (2–3)	0.91
Socio-economic status (IRSAD)			
Lowest quintile	6 (19.4)	22 (6.2)	0.02
Highest quintile	3 (9.7)	51 (14.3)	0.56
Pre-existing conditions			
Lupus nephritis	11 (35.5)	47 (13.2)	<0.01
PE/DVT	3 (9.7)	5 (1.4)	0.02
Diabetes mellitus	3 (9.7)	7 (2.0)	0.04
Tobacco use	6 (19.4)	25 (7.0)	0.04

Figures are median with IQR or number (%) for indigenous Australian (IA) and non-indigenous (NI) patients with lupus.

DVT, deep vein thrombosis; IRSAD, Index of Relative Socio-Economic Advantage and Disadvantage; IQR, interquartile range; PE, pulmonary embolism.

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Table 2 Pregnancy outcomes in women with systemic lupus erythematosus by cultural background

Outcome	IA ($n = 62$)	NI ($n = 640$)	OR (95% CI)	P value
Terminated pregnancy ($n = 138$)	<5 (4.8)	135 (21.1)	0.19 (0.05–0.55)	<0.01
Continued pregnancy ($n = 564$)	59 (95.2)	505 (78.9)		
Live births	50 (84.7)	462 (91.5)	0.52 (0.24–1.19)	0.15
Pregnancy loss	9 (15.3)	43 (8.5)	1.75 (0.76–3.72)	
Spontaneous abortion	8 (13.5)	35 (6.9)	1.91 (0.79–4.10)	0.13
Stillbirth	<5 (1.7)	8 (1.6)	0.99 (0.04–6.38)	0.99
Continued pregnancy with†				
Preterm delivery	6 (12)	62 (13.4)	0.86 (0.32–2.01)	0.98
Caesarean delivery	15 (30)	218 (47.2)	0.47 (0.24–0.87)	0.02
Fetal growth restriction	<5 (6)	22 (4.8)	0.82 (0.13–3.11)	0.67
(Pre-) eclampsia	<5 (8)	46 (9.9)	0.56 (0.14–1.71)	0.89
Gestational diabetes	13 (26)	28 (6.1)	5.27 (2.46–10.97)	<0.01
Infection	11 (22)	29 (6.3)	4.09 (1.84–8.71)	<0.01
Renal flare	10 (20)	26 (5.6)	4.07 (1.76–8.94)	<0.01
PE/DVT	<5 (6)	8 (1.7)	2.31 (0.32–10.33)	0.16
Postpartum bleeding w/transfusion	-	<5 (0.6)	NA	NA
Maternal death	-	<5 (0.2)	NA	NA

†No. live births as denominator.

Figures are numbers (%) and OR (odds ratio) with 95% confidence intervals (CIs) that indicate odds for indigenous Australian (IA) versus non-indigenous (NI) patients with lupus.

Small numbers are presented as <5 as per HREC requirements to prevent possible identification.

95% CI: 1.84–8.71, $P < 0.001$) and renal flares (4.07, 95% CI: 1.76–8.94, $P < 0.001$); however, there were no maternal deaths among IA patients.

Discussion

Over the last decades, the elimination of perceived barriers has led to steady increases in the number of pregnancies among women with lupus, as borne out by the increasing numbers of lupus pregnancies over time in this study.[16,17] The results of this study indicate a higher burden of pre-existing comorbidity and maternal pregnancy complications in IA patients, although this was not associated with a significantly lower LB or higher PB rate.

There has been a gradual but significant decline in lupus pregnancy loss rates, with LB rates reported between 70% and 85% in recent decades in various patient populations.[18–21] The 73.4% overall LB rate for Australian patients with lupus falls well within this range, and while there was an increase in LB to nearly 80% for NI patients over time, no such improvement was seen for IA patients, similar to findings in black patients with lupus in the USA, suggesting socio-economic rather than disease-specific factors were key contributors to APO disparities.[7,22] Rates for spontaneous abortion and SB rates were in line with current literature on lupus pregnancies and similar for IA and NI patients with lupus.[19,23,24] However, pregnancy termination was much higher in NI patients, which is not dissimilar to recent data from Canada[25] and to rates in the general Australian population over the study period.[26] With few absolute medical contraindications for planned pregnancy in quiescent lupus, the high rate of pregnancy termination in NI patients with lupus, albeit decreasing over time, suggests a need to improve pre-pregnancy counselling by encouraging adherence to and/or referring patients for contraception considering the potentially teratogenic effects of medication. Our administrative outcome data unfortunately cannot clarify whether logistical, medical or sociocultural considerations underpin the differences in pregnancy termination between IA and NI patients with lupus.

Fetal growth restriction (FGR) is a result of complex maternal and fetal factors. FGR was seen in 4.8% of patients with lupus, confirming an overall higher prevalence in patients with lupus than the general population,[1] and the slightly higher rate in IA patients is in line with findings in black patients with lupus.[5] The frequency of spontaneous or medically induced preterm births (PBs) is 5–9% in developed countries,[27] and the higher PB frequency in lupus patients reported here (12.1%) aligns with other studies, although higher PB rates have been reported in the USA for patients with lupus and the general population.[17,19,28] The combination of lupus with a maternal adverse pregnancy outcome may well increase the risk for perinatal morbidity resulting in prematurity.[27] Pre-eclampsia is one of the most severe pregnancy complications with a global prevalence of 4.6%[29]; the nearly 10% prevalence in this and

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other studies confirm the much higher risk with lupus.[5,19] Surprisingly, pre-eclampsia was not more frequent in IA patients with lupus despite a much higher rate of renal involvement and diabetes, although this may have been counteracted by higher tobacco use, which lowers pre-eclampsia risk.[30] Although lupus nephritis is generally considered a risk factor for APO, it has been shown that lupus nephritis activity at the onset of pregnancy rather than a history of lupus nephritis is the major determinant of pregnancy outcome.[31–33] Furthermore, we cannot exclude that the well-known difficulty of distinguishing between a renal lupus flare and pre-eclampsia has confounded our data. Our data also indicate a high level of gestational diabetes in patients with lupus overall, with higher rates in IA compared to NI patients with lupus (16% vs 6%). Although the contribution of steroid use during pregnancy to manage symptoms cannot be excluded, this likely reflects the observed increase in gestational DM in the general WA population in recent decades.[34]

The limitations of this study relate to the use of administrative health data and include the lack of clinical details such as lupus disease activity measures, laboratory findings and medication use in mothers, whereas we did not have neonatal data such as exact birth weight. The small number of pregnancies in IA patients with lupus limited more advanced statistical analyses of risk factors for APO and we could not assess whether compared to NI patients, healthcare engagement was different for IA patients, who more often live remotely. The strength of this study includes the long-term population-wide design, leading to one of the largest lupus pregnancy cohorts reported and the first study to report on IA lupus pregnancies. Also, the use of pregnancy-related variables recorded in administrative databases has been found to be highly valid as compared to medical chart review.[35]

Conclusion

We observed a significantly higher burden of maternal comorbidities and renal disease burden in pregnant IA patients with lupus. While PB rates in this lupus cohort were overall high, they were similar for IA and NI lupus pregnancies and LB rates also did not differ significantly. While comprehensive preconception advice can reduce the need for pregnancy terminations, close monitoring for maternal complications will be required to further reduce maternal and fetal APO in all lupus patients.

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Ethics Statement

This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendment. Approval for the use of de-identified data was obtained from the Human Research Ethics Committee at the WA Department of Health (WADOH HREC# 2016.24).

Data Availability Statement

The data that support the findings of this study were used under licence from the WA Health Data Linkage Branch. Restrictions apply to the availability of these data, but upon reasonable request and following permission of WA Health and WA Data Linkage Branch, data are available from the authors.

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