Evidence of under-reporting of early-onset preeclampsia using register data

Julia F. Simard1,2,3 | Marios Rossides3 | Anna-Karin Wikström3,4 | Titilola Falasinnu1 | Kristin Palmsten5 | Elizabeth V. Arkema3

1Department of Epidemiology and Population Health, Stanford Medicine, Stanford, CA, USA
2Division of Immunology and Rheumatology, Department of Medicine, Stanford Medicine, Stanford, CA, USA
3Clinical Epidemiology Division, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden
4Department of Women’s and Children’s Health, Uppsala University, Stockholm, Sweden
5HealthPartners Institute, Minneapolis, MN, USA

Correspondence
Julia Fridman Simard, Department of Epidemiology and Population Health, Department of Medicine – Immunology & Rheumatology, Stanford University, Stanford, CA, USA.
Email: jsimard@stanford.edu

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Abstract
Background: Early-onset preeclampsia, traditionally defined as presenting before 34 gestational weeks, is associated with even higher risks of perinatal death, placental abruption, and stroke, than late-onset preeclampsia.

Objective: We estimated the degree of misclassification in a high-risk population of lupus pregnancies and a general population comparator when gestational age at delivery defined preeclampsia phenotype compared to first preeclampsia diagnosis.

Methods: Patients with lupus and general population comparators from Sweden with ≥1 singleton pregnancy in the Medical Birth Register with a documented ICD code for preeclampsia were included (2002-2016). We used gestational age at delivery (<34 versus ≥34 weeks) to phenotype preeclampsia early- versus late-onset and then reclassified based on first preeclampsia diagnosis date in the Patient Register. We cross-tabulated the two definitions and calculated sensitivity using the visit-based definition as the reference standard for general population and lupus pregnancies, overall and among nulliparous women.

Results: 331 pregnancies were diagnosed with preeclampsia, of which 322 were in both registers. Of those, 58 were early-onset based on gestational age at delivery (n = 29 in lupus pregnancies). Overall, 9% of early-onset preeclampsia in lupus (sensitivity 91%, 95% confidence interval [CI] 75, 98) was misclassified as late-onset compared to 19% in the general population (sensitivity 81%, 95% CI 64, 92). We noted similar misclassification (4% vs 22%) among nulliparous women.

Conclusions: In the general population, early-onset preeclampsia was more likely misclassified as late-onset than in the high-risk lupus population. Relying on gestational age at delivery to phenotype preeclampsia, this way underestimates the occurrence of early-onset preeclampsia. This also suggests that the burden of early-onset preeclampsia as a public health concern may be under-reported, although this may be more applicable to milder preeclampsia where expectant management is employed. Research of biological and maternal predictors of early-onset preeclampsia may be dealing with differentially misclassified outcomes or samples.

Keywords
early-onset preeclampsia, misclassification, preeclampsia, registers

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1 | INTRODUCTION

Preeclampsia is a significant maternal complication contributing to maternal morbidity and death and posing risks to the foetus and offspring.1 Some chronic diseases, such as systemic lupus erythematosus, increase the risk for preeclampsia. We recently showed that women with lupus had between a four and seven-fold increased risk of early-onset preeclampsia compared to women from the general population in Sweden.2

Early-onset preeclampsia, defined as presenting before 34 gestational weeks, is reportedly associated with a higher risk of placental abruptions, stroke, acute respiratory distress, and foetal or perinatal death in comparison to late-onset preeclampsia.3 Some have suggested that the underlying causes, risk factors, and immunology of these preeclampsia phenotypes differ.4,5 Despite interest in understanding and preventing early-onset preeclampsia, no single definition is used in practice or in research.6,7 In epidemiologic research restricting to birth certificate data, maternal self-report, or delivery discharge data, it is not uncommon to use gestational age at delivery to phenotype preeclampsia despite the fact that delivery may be delayed while a case is monitored.8,9 Consequently, as Lisonkova and Joseph noted,10 the true burden of early-onset preeclampsia may be underestimated, impacting research of this important contributor to maternal and neonate morbidity and mortality.

We present an alternative approach leveraging multi-faceted Swedish register data to quantify the degree of misclassification of early versus late preeclampsia in both high-risk and general populations and discuss the implications of this potential misclassification to research.

2 | METHODS

2.1 | Setting and data

Women from the Swedish Lupus Linkage (SLINK) cohort with at least one birth registered in the Medical Birth Register (MBR) between 2002 and 2016 were included in the study.11 The MBR includes reproductive history and diagnoses during pregnancy on nearly all births in Sweden but without diagnosis dates. Prevalent lupus was defined as a history of ≥2 visits in the National Patient Register (NPR) with a lupus-coded diagnosis using ICD codes with ≥1 from a specialist versed in lupus. Women from the Swedish general population in SLINK and their corresponding pregnancies during this time were included as the comparator. We included only singleton pregnancies and identified 964 lupus pregnancies and 8733 general population pregnancies.

In Sweden, midwives provide routine prenatal care including blood pressure and proteinuria monitoring. Women with preeclampsia are monitored by specialists in obstetrics and gynaecology who report diagnoses and dates of outpatient visits and inpatient admission to the NPR.

2.2 | Classifying preeclampsia/eclampsia

Preeclampsia was defined using ICD-10 codes (O11, O14, and O15 including all subcategories) and classified as early-onset on the basis of a 34-week gestation cut-point. First using the MBR, gestational age at delivery was used to define early-onset versus late-onset preeclampsia (87 preeclampsia exposed pregnancies in lupus and 244 in the general population comparator). Among these 331 deliveries with a maternal preeclampsia diagnosis, we applied a second visit-based definition, using the first preeclampsia-coded visit in the NPR during the pregnancy. Visit-based early-onset preeclampsia was present if the first preeclampsia ICD inpatient/outpatient visit in the NPR was before 34 weeks (LMP + 238 days). 87 of 87 lupus pregnancies had preeclampsia listed in both registers, while 235 (96%) of 244 from the general population were in both MBR and NPR.

2.3 | Statistical analysis

Preeclampsia phenotype (early versus late-onset) according to register source was cross-tabulated among those in both the NPR and MBR, separately for lupus and general population pregnancies. We compared pregnancy duration for these pregnancies using the two data sources. Sensitivity and exact binomial 95% confidence intervals were calculated using the visit-based definition of preeclampsia.
phenotype as the reference as it most closely reflected onset. We calculated the proportion of early-onset preeclampsia misclassified as late-onset in the two populations separately.

For the pregnancies with preeclampsia-coded deliveries in the MBR without a corresponding NPR diagnosis, we conducted a sensitivity analysis assuming preeclampsia was the indication for delivery and gestational age appropriately represented diagnosis/onset timing.

3 | RESULTS

During the study period, 331 singleton pregnancies were diagnosed with preeclampsia in our study population in the MBR. The majority were among our general population comparator (244 with preeclampsia out of 8733 women, 2.8%). However, there were 87 lupus pregnancies also complicated by preeclampsia (9.0% of the prevalent lupus group). There were subtle differences between the women with lupus and those from the general population (Table 1).

Comparing pregnancy duration at preeclampsia presentation from these two data sources, results were similar, however, as expected, the gestational age at assumed preeclampsia onset was lower when using the NPR visit/admission date in both SLE and general population pregnancies. Using gestational age at delivery to estimate preeclampsia onset, the earliest onset was 23 weeks in lupus pregnancies and 26 weeks in the general population, compared to onset estimated by first visit/admission in the NPR of 22 weeks and 23 weeks, respectively. In the general population, early-onset preeclampsia presented on average during gestational week 30 (median, week 31), whereas in the women with lupus, it presented at an average of 28 gestational weeks (median, week 29.5). The median difference between first preeclampsia visit/admission and delivery date was one day in both groups.

Overall, among the 322 singleton pregnancies with preeclampsia in both sources in our study population (97% of those with preeclampsia in the MBR), there were 58 pregnancies with early-onset preeclampsia based on gestational age at delivery (29 were lupus-exposed). However, when using the visit-based definition an additional 10 cases were identified (Table 2). Three of 32 (9%) of early-onset preeclampsia in lupus were misclassified as late-onset compared to nearly 19% (7 of 36) in the general population (corresponding to sensitivities of 91%, 95% CI 75, 98, and 81%, 95% CI 64, 92, respectively). Among the 10 early-onset misclassified as late-onset (3 SLE, 7 general population), the difference between first preeclampsia visit/admission and delivery date ranged from days to weeks (Table 3). When looking exclusively among nulliparous women, we found that the sensitivity decreased among the general population (78%, 95% CI 56, 93) but increased in the lupus population (96%, 95% CI 79, 100) among first deliveries.

In a sensitivity analysis including pregnancies with no NPR preeclampsia diagnoses (n = 9), the sensitivity and specificity were unchanged as these were all from the general population with a mean gestational age of 39 weeks ± 6 days and ranged from 38 to 42 gestational weeks.

### Study population characteristics

|                        | SLE (n = 87) | General population (n = 235) |
|------------------------|-------------|-----------------------------|
| Age at delivery, years | 31.4 (4.9)  | 32.1 (5.1)                  |
| Maternal birth country |             |                             |
| Sweden                 | 77 (89)     | 203 (86)                    |
| Other, Nordic          | 2 (2)       | 3 (1)                       |
| Other, non-Nordic      | 8 (9)       | 29 (12)                     |
| Missing                | 0 (0)       | 0 (0)                       |
| Parity                 |             |                             |
| First pregnancy/birth  | 58 (67)     | 148 (63)                    |
| Subsequent pregnancy/ birth | 29 (33) | 87 (37)                     |
| Calendar year of delivery |          |                             |
| 2002-2009              | 43 (49)     | 138 (59)                    |
| 2010-2016              | 44 (51)     | 97 (41)                     |
| Maternal BMI, kg/m²²   |             |                             |
| Meana                  | 25.5 (4.7)  | 27.0 (5.3)                  |
| Underweight (<18.5)    | 2 (2)       | 2 (<1)                      |
| Normal (18.5-24.9)     | 39 (45)     | 92 (39)                     |
| Overweight (25.0-29.9) | 19 (22)     | 57 (24)                     |
| Obese (≥30.0)          | 11 (13)     | 52 (22)                     |
| Missing                | 16 (18)     | 32 (14)                     |
| Maternal self-reported current smoking during first trimester |          |                             |
| Yes                    | 5 (6)       | 8 (3)                       |
| No                     | 69 (79)     | 212 (90)                    |
| Missing                | 13 (15)     | 15 (6)                      |
| History of preeclampsia in ≥1 previous pregnancyb | 10/29 (34) | 31/87 (36) |

Abbreviations: BMI, body mass index; SD, standard deviation. Data are mean (standard deviation) or n (%) or n/N (%). Category percentages may not sum up to 100 owing to rounding.

Excluding missing.

Evaluated in subsequent pregnancies/births and defined using data from the Medical Birth Register and/or the National Patient Register.

3.1 | Comment

In the general population, early-onset preeclampsia was more likely to be misclassified as late-onset than in the high-risk lupus population among all births (19% vs. 9%). Among nulliparous women, the difference persisted (22% vs. 4%). It may be that in the presence of a high-risk maternal comorbidity such as lupus, physicians are less likely to delay delivery and therefore onset and delivery dates are closer, or that their preeclampsia is more severe. Pregnant women with lupus also presented with preeclampsia earlier than the general population, possibly making it harder to delay to 34 weeks.

In the lupus pregnancies, few were reclassified when using first visit/hospitalisation date although early-onset preeclampsia
accounted for more than 37% of the events. This may not be surprising as a lupus diagnosis often requires careful monitoring during pregnancy, even in Sweden where the majority of prenatal care is administered by midwives. The differences between the lupus and the general population pregnancies may be biological with respect to preeclampsia aetiology, as well as surveillance bias. Although increased detection may be a source of bias in the lupus setting, Swedish prenatal care is thorough and by protocol, including screening for hypertension and related factors for all women. Further, given that severe preeclampsia is more likely to necessitate immediate delivery, our findings may apply more to milder preeclampsia, which may be more common in the general population.

The International Society for the Study of Hypertension in Pregnancy guidelines recommend categorisation into early- and late-onset preeclampsia. However, the definition of early-onset preeclampsia is not uniform across studies. This lack of standardisation can lead to discrepancies in the reported prevalence and management of this condition. In our study, we compared two definitions of early and late preeclampsia: one based on gestational age at delivery and the other based on the first visit in the patient register with preeclampsia. The results are presented in Table 2.

### Table 2: Reclassification comparing two definitions of early and late preeclampsia (gestational age at delivery versus first visit in the patient register with preeclampsia), overall and stratified by parity

|            | General population (n = 235) | SLE population (n = 87) |
|------------|-----------------------------|------------------------|
|            | Visit-based definition (National Patient Register) | Visit-based definition (National Patient Register) |
|            | Early | Late | All | Early | Late | All |
| Gestational age-based definition (Medical Birth Register) | Early | 29 | 0 | 29 | Gestational age-based definition (Medical Birth Register) | Early | 29 | 0 | 29 |
|            | Late | 7 | 199 | 206 | Late | 3 | 55 | 58 |
|            | All | 36 | 199 | 235 | All | 32 | 55 | 87 |
| Sensitivity (95% CI) | 81 (64, 92) | Sensitivity (95% CI) | 91 (75, 98) |

|            | General population (n = 148) | SLE population (n = 58) |
|------------|-----------------------------|------------------------|
|            | Visit-based definition (National Patient Register) | Visit-based definition (National Patient Register) |
|            | Early | Late | All | Early | Late | All |
| Gestational age-based definition (Medical Birth Register) | Early | 18 | 0 | 18 | Gestational age-based definition (Medical Birth Register) | Early | 23 | 0 | 23 |
|            | Late | 5 | 125 | 130 | Late | 1 | 34 | 35 |
|            | All | 23 | 125 | 148 | All | 24 | 34 | 58 |
| Sensitivity (95% CI) | 78 (56, 93) | Sensitivity (95% CI) | 96 (79, 100) |

### Table 3: Estimated gestational weeks across both sources (Medical Birth Register and National Patient Register) for the 10 misclassified early-onset preeclampsia cases

|            | Gestational weeks at delivery from the MBR | Gestational weeks when preeclampsia was diagnosed in the NPR |
|------------|------------------------------------------|----------------------------------------------------------|
| SLE        |                                          |                                                          |
| S1         | 34 + 1                                   | 33 + 5                                                   |
| S2         | 34 + 6                                   | 33 + 4                                                   |
| S3         | 38 + 0                                   | 30 + 3                                                   |
| General population | | |
| G1         | 34 + 0                                   | 32 + 3                                                   |
| G2         | 34 + 4                                   | 33 + 1                                                   |
| G3         | 36 + 4                                   | 33 + 3                                                   |
| G4         | 37 + 3                                   | 23 + 0                                                   |
| G5         | 37 + 3                                   | 31 + 0                                                   |
| G6         | 39 + 6                                   | 32 + 0                                                   |
| G7         | 41 + 2                                   | 24 + 1                                                   |

Abbreviations: MBR, Medical Birth Register; NPR, National Patient Register.
late-onset disease, and we show that we cannot use date of delivery as a proxy of onset. Some have addressed this issue by using the date of inpatient admission with preeclampsia, which addresses some, but not all, of the bias. Inpatient admission is likely associated with delivery, which may make the lag between admission and delivery smaller than the lag between first visit with preeclampsia and delivery. This is largely impacted by how commonly early-onset preeclampsia is monitored in the outpatient setting, which may vary by comorbidity and other factors. We are undercounting early-onset preeclampsia in research, although clinically we anticipate that care providers know that these women are developing preeclampsia early and act accordingly.

The impact of this misclassification extends beyond register-based studies and analyses of preeclampsia phenotypes in big data. We have shown that using gestational age at delivery to define early-onset preeclampsia underestimates its occurrence and may incorrectly misclassify it as late-onset preeclampsia. Studies attempting to identify biological and maternal predictors of early-onset vs late-onset preeclampsia will inadvertently contaminate the late-onset phenotype comparator. This also applies to phenotyping into more categories (eg early (<34 weeks), intermediate (34-37 weeks), and late (≥38 weeks)) on the basis of gestational age at delivery. This concern extends to any research using gestational age at delivery to define preeclampsia phenotypes, including studies of placental tissue or any—omics analyses. Our study focused on comparing two different data-based definitions and did not have medical records to confirm the diagnoses, nor sufficient power to explore secular trends.

4 | CONCLUSIONS

These findings have strong repercussions for allocating resources if the aetiologies are, indeed, different. Further, this misclassification appeared to be differential by maternal morbidity and may be considerable (nearly 1 in 5) in the general population. Data from this study and similar work in more heterogeneous population may be used in probabilistic sensitivity analyses and other approaches to account for the misclassification when data on gestational age at delivery are used to define early-onset preeclampsia.

CONFLICT OF INTEREST

MR has received non-promotional speaker fees from Teva Pharmaceuticals, outside the submitted work. None of the other authors report any conflict.

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