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ORIGINAL ARTICLE

Proteinuria and venous thromboembolism in pregnancy: a population-based cohort study

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ABSTRACT

Background. Pregnancy-associated venous thromboembolism (VTE) is associated with high morbidity and mortality. Identification of risk factors of VTE may lead to improved maternal and foetal outcomes. Proteinuria confers a pro-thrombotic state, however, its association with VTE in pregnancy remains unknown. We set out to assess the association of proteinuria and VTE during pregnancy.

Methods. We conducted a population-based, retrospective cohort study of all pregnant women (≥16 years of age) with a proteinuria measure within 20 weeks of conception ($n = 306\,244$; mean age 29.8 years) from Ontario, Canada. Proteinuria was defined by any of the following: urine albumin:creatinine ratio ≥3 mg/mmol, urine protein:creatinine ratio ≥5 mg/mmol or urine dipstick proteinuria ≥1. The main outcome measure was a diagnosis of VTE up to 24-weeks post-partum.

Results. A positive proteinuria measurement occurred in 8508 (2.78%) women and was more common with a history of kidney disease, gestational or non-gestational diabetes mellitus and hypertension. VTE events occurred in 625 (0.20%) individuals, with a higher risk among women with positive proteinuria [32 events (0.38%)] compared with women without proteinuria [593 events (0.20%); inverse probability-weighted risk ratio 1.79 (95% confidence interval 1.25–2.57)]. The association was consistent using a more specific VTE definition, in the post-partum period, in high-risk subgroups (hypertension or diabetes) and when the sample was restricted to women with preserved kidney function.

Conclusions. The presence of proteinuria in the first 20 weeks of pregnancy is associated with a significantly higher risk of VTE.

Keywords: kidney function, pregnancy, pre-eclampsia, proteinuria, venous thromboembolism

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INTRODUCTION

The fifth leading cause of pregnancy-related death (accounting for 9%) in the USA is pregnancy-related venous thromboembolism (VTE), a complication with an estimated incidence of 2.7–12.2/10 000 pregnancies [1–3]. As VTE is highly preventable through the prudent use of anticoagulant therapy, risk assessment and the identification of key risk factors will lead to improved maternal and foetal outcomes. Identified key risk factors for pregnancy-related VTE include factors based on timing (increasing markedly 15- to 35-fold in the immediate 6 weeks post-partum), pre-existing conditions (autoimmune disease and thrombophilia) or pregnancy-related complications (pre-eclampsia) [4–7].

Proteinuria is emerging as a recognized risk factor for thromboembolism. Multiple epidemiologic studies to date in non-pregnant populations report an independent, dose-dependent association between proteinuria and an elevated VTE risk [8–11]. The presence of proteinuria may serve as a warning signal for high-risk pregnancies and identify individuals who require more frequent monitoring [4]. We hypothesized that the presence of proteinuria would be associated with a higher risk of VTE in pregnancy. As such, we conducted a population-based retrospective cohort study to determine the association of proteinuria and VTE in pregnant women over a 10-year period in Ontario, Canada.

MATERIALS AND METHODS

Design, setting and data sources

We conducted a population-based cohort study of pregnant women with a delivery using de-identified linked databases housed at the Institute for Clinical Evaluative Sciences (ICES) (see Supplementary data, Table S1 for a description of the databases used in this study) [12]. Ontario is Canada's largest province, with >14.7 million residents [13]. Demographic and vital statistics information was obtained from the Ontario Registered Persons Database. Pregnancy and maternal health data were captured in the MOMBABYdataset that links administrative records of all mothers with a delivery and their newborns across Ontario [14]. Diagnostic and procedural information from all hospitalizations was determined using the Canadian Institute for Health Information (CIHI) Discharge Abstract Database (DAD). Diagnostic information from emergency room visits was determined using the National Ambulatory Care Reporting System. Information was also obtained from the Ontario Health Insurance Plan database, which contains all claims for inpatient and outpatient physician services. Whenever possible, we defined patient characteristics and outcomes using validated codes (see Supplementary data, Table S2). The use of data in this project was authorized under Section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a research ethics board. The reporting of this study follows the Reporting of Studies Conducted Using Observational Routinely Collected Health Data guidelines for observational studies (see Supplementary data, Table S3) [15].

Study population

All pregnant women ≥16 years of age from 2007 to 2016 in Ontario, Canada (see Supplementary data, Figure S1 for cohort creation) with a delivery (live and non-live births) were included in the analysis ($n = 824\,324$). Exclusion criteria were missing gestational age ($n = 62$), no proteinuria measure prior to 20 weeks gestation ($n = 517\,546$) and previous kidney transplantation ($n = 35$) or being on dialysis ($n = 56$). We excluded proteinuria measures after 20 weeks to limit proteinuria associated with pre-eclampsia. This population is made up of women who conceived and had a delivery in hospital and did not capture spontaneous terminations that did not result in a delivery or pregnancies among those who had a home delivery. Individuals were censored at first occurrence of death, study outcome, 24 weeks post-delivery, loss to follow-up or end of the study period (31 December 2019; see Supplementary data, Figure S2 for the study cohort design diagram).

Exposure and covariates

The study exposure was the presence of proteinuria, defined by any of the following: a urine dipstick proteinuria ≥1+, a urine albumin:creatinine ratio ≥3 mg/mmol or a protein:creatinine ratio ≥5 mg/mmol measured prior to 20 weeks gestation [16]. The study index date was the first proteinuria measure after the estimated conception date. If multiple measures were present, the most recent was used. Potential confounders examined included demographics (age, income and place of residence), index year (the year of delivery), previous live births, previous comorbid illnesses (history of gestational diabetes, pre-eclampsia, gestational hypertension, acute kidney injury, chronic kidney disease, major haemorrhage, hypertension, diabetes, stroke, atrial fibrillation, acute coronary syndrome, heart failure, cardiovascular disease, previous VTE, cancer, lupus, rheumatoid arthritis, Crohn's/ulcerative colitis, liver disease and drug dependency/tobacco use), Charlson comorbidity index, healthcare utilization (hospitalizations, recent surgery prior to the index date) and baseline estimated glomerular filtration rate (eGFR).

Outcomes

The study outcome was a deep vein thrombosis (DVT) or pulmonary embolism (PE), defined as follows: a diagnostic or physician billing code during hospitalization, emergency department or outpatient visit (see Supplementary data, Table S2 for full data definitions). In a sensitivity analysis, we examined a more specific VTE outcome defined as the criteria above plus related radiological imaging within a hospital admission or 7 days from a physician billing code or ambulatory/emergency room visit [17]. This definition was validated with a sensitivity, specificity, positive likelihood ratio and positive predictive value of 94, 75, 12 and 73%, respectively [17]. A diagnostic code for PE was examined and combined into VTE due to the small number of events.

Statistical analysis

We used standardized differences to assess baseline characteristics by exposure status (presence versus absence of proteinuria). Standardized differences describe differences between group means relative to the pooled standard deviation, are less sensitive to large sample sizes than traditional hypothesis testing and a significant difference is considered to be ≥10% [18]. To estimate the exposure-attributable effect of a positive proteinuria measure on VTE, we calculated the risk difference between individuals with and without proteinuria. The risk difference provides an absolute measure of effect (how many additional VTE events can be attributed to a positive proteinuria measure) [19]. To determine a relative measure of effect (the odds ratio, which for rare events is equivalent to the rate ratio), we used generalized linear models (GLMs) specified as the logit link function [20]. To account for confounding between exposure

Table 1. Baseline characteristics by the presence and absence of proteinuria measured up to 20 weeks during pregnancy

Characteristics	Total, *n* (%)	Proteinuria		Standardized difference[a], %
		Present, *n* (%)	Absent, *n* (%)	
N	306 244	8510	297 734	
Demographics				
Age (years)				
Mean ± SD	29.84 ± 5.32	29.42 ± 5.74	29.85 ± 5.31	8
Median (25–75th percentile)	30 (26–33)	30 (25–33)	30 (26–33)	7
<30	142 464 (46.5)	4186 (49.2)	138 278 (46.4)	5
30–40	158 003 (51.6)	4150 (48.8)	153 853 (51.7)	6
>40	5777 (1.9)	174 (2.0)	5603 (1.9)	1
Year of cohort entry	1653 (0.5)	80 (0.9)	1573 (0.5)	5
2007	21 348 (7.0)	1064 (12.5)	20 284 (6.8)	19
2008	30 898 (10.1)	1321 (15.5)	29 577 (9.9)	17
2009	40 132 (13.1)	1168 (13.7)	38 964 (13.1)	2
2010	40 323 (13.2)	901 (10.6)	39 422 (13.2)	8
2011	45 069 (14.7)	919 (10.8)	44 150 (14.8)	12
2012	46 025 (15.0)	966 (11.4)	45 059 (15.1)	11
2013	46 015 (15.0)	1055 (12.4)	44 960 (15.1)	8
2014	33 582 (11.0)	914 (10.7)	32 668 (11.0)	1
2015	1199 (0.4)	122 (1.4)	1077 (0.4)	11
2016	900 (0.3)	27 (0.3)	873 (0.3)	0
Income quintile				
1—Lowest	68 362 (22.3)	2302 (27.1)	66 060 (22.2)	11
2	63 015 (20.6)	1769 (20.8)	61 246 (20.6)	1
3	63 055 (20.6)	1789 (21.0)	61 266 (20.6)	1
4	64 510 (21.1)	1568 (18.4)	62 942 (21.1)	7
5—Highest	46 402 (15.2)	1055 (12.4)	45 347 (15.2)	8
Rural residence	22 775 (7.4)	487 (5.7)	22 288 (7.5)	7
Previous live births (parity)				
0	161 680 (52.8)	4304 (50.6)	157 376 (52.9)	5
1	94 320 (30.8)	2688 (31.6)	91 632 (30.8)	2
2	34 001 (11.1)	992 (11.7)	33 009 (11.1)	2
≥3	14 412 (4.7)	451 (5.3)	13 961 (4.7)	3
Missing	1831 (0.6)	75 (0.9)	1756 (0.6)	3
Recent surgery (within 3 months)	6543 (2.1)	212 (2.5)	6331 (2.1)	2
Gestational diabetes	15 597 (5.1)	752 (8.8)	14 845 (5.0)	15
Pre-eclampsia	6494 (2.1)	310 (3.6)	6184 (2.1)	9
Gestational hypertension	5106 (1.7)	222 (2.6)	4884 (1.6)	7
Chronic kidney disease	462 (0.2)	124 (1.5)	338 (0.1)	15
Acute kidney injury	128 (0.0)	20 (0.2)	108 (0.0)	5
Diabetes	7058 (2.3)	459 (5.4)	6599 (2.2)	17
Hypertension	8765 (2.9)	485 (5.7)	8280 (2.8)	15
Previous VTE	2613 (0.9)	89 (1.0)	2524 (0.8)	2
Cardiovascular disease	1225 (0.4)	47 (0.6)	1178 (0.4)	2
Atrial fibrillation	42 (0.0)	≤6[b] (0.0)	36–42[b] (0.0)	1
Heart failure	≤6[b] (0.0)	0 (0.0)	≤6[b] (0.0)	1
Baseline major haemorrhage	2380 (0.8)	55 (0.6)	2325 (0.8)	2
Cancer	13 972 (4.6)	397 (4.7)	13 575 (4.6)	1
Lupus	6039 (2.0)	198 (2.3)	5841 (2.0)	3
Rheumatoid arthritis	2634 (0.9)	74 (0.9)	2560 (0.9)	0
Crohn's/ulcerative colitis	2756 (0.9)	73 (0.9)	2683 (0.9)	0
Chronic liver disease	7541 (2.5)	257 (3.0)	7284 (2.4)	4
Drug dependence or tobacco use	15 420 (5.0)	454 (5.3)	14 966 (5.0)	1
Charlson comorbidity index				
0	135 673 (44.3)	3841 (45.1)	131 832 (44.3)	2
1	2948 (1.0)	181 (2.1)	2767 (0.9)	10
≥2	1244 (0.4)	91 (1.1)	1153 (0.4)	8
No hospitalizations	166 379 (54.3)	4397 (51.7)	16 1982 (54.4)	5
Laboratory measurements 1 year prior to index date				
eGFR (mL/min/1.73 m^2)				
≥90	157 617 (51.5)	4842 (56.9)	152 775 (51.3)	11
≥60–<90	5206 (1.7)	203 (2.4)	5 003 (1.7)	5
≥30–<60	122 (0.0)	29 (0.3)	93 (0.0)	7
<30	20 (0.0)	11 (0.1)	9 (0.0)	5

[a]A standardized difference of 10% was considered statistically significant.
[b]Small cells are not reported as per ICES policy; where back calculation may occur a range is provided.

groups, we used inverse probability of treatment weighting (IPTW) [21]. IPTW was the preferred approach, as it retains all eligible cases for analysis. The IPT weights were calculated using all baseline covariates listed in Table 1 and were truncated at the 1st and 99th percentiles. Variance estimates for the GLMs were obtained using the robust sandwich estimator. Only the first VTE outcome was considered. We conducted a number of additional analyses. First, as the post-partum period is known to be associated with a higher VTE risk, we stratified our models by the pre-/post-partum periods [5]. For these analyses, the delivery date was included in the post-partum period. Second, we examined whether early proteinuria was associated with VTE risk, thus we limited our models to proteinuria measures obtained within the first trimester (12 weeks after the conception date). Third, as proteinuria is common with kidney diseases that may lead to reductions in eGFR, we limited our models to women with normal kidney function only (eGFR $\geq$90 mL/min/1.73 m^2). Baseline eGFR was available in 53% of the study cohort. Lastly, we examined the association of proteinuria and VTE in high-risk subgroups of pregnancies with hypertension/gestational hypertension and diabetes mellitus/gestational diabetes. We conducted all analyses with SAS software version 9.4 (SAS Institute, Cary, NC, USA). Confidence intervals (CIs) that did not overlap with 1 were treated as statistically significant.

Ethics

The use of data in this project was authorized under Section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a research ethics board.

RESULTS

A total of 824 324 unique women delivered during the study period with a proteinuria measure in 306 716 (37.2%) and 625 (0.20%) VTE events. After exclusions, the final study cohort comprised 306 244 women with proteinuria detected in 2.8% (8510) and an absence of proteinuria in 97.2% (297 734). Women with and without proteinuria were similar in mean age, age distribution, place of residence, previous live births and recent surgeries or fractures. Women with proteinuria were more common in the lowest income quintile and more likely to have gestational diabetes, chronic kidney disease, diabetes and pre-existing hypertension (Table 1). After weighting there was a balance between the two groups (no standardized differences >10%).

VTE events were 1.8-fold more common in women with proteinuria relative to those without proteinuria [proteinuria 32 events (0.38%) versus no proteinuria 593 (0.20%) events]. Proteinuria was associated with an attributable risk difference of an additional 15.7 VTE cases/10 000 person-years of follow-up. The higher VTE risk was consistent in weighted analyses with a relative risk (RR) of 1.79 [95% confidence interval (CI) 1.25–2.57] (see Table 2).

When using a more specific, validated VTE definition, a total of seven events were observed with a roughly 4-fold increase in VTE risk with proteinuria [proteinuria 7 (0.09%) events versus no proteinuria 67 (0.02%) events] that was consistent in weighted analyses [IPT weighted RR 3.73 (95% CI 1.70–8.21)].

Women with proteinuria had a higher relative risk of VTE in the post-partum period [post-partum RR 2.22 (95% CI 1.43–3.44)] with no higher risk in the pre-partum period (see Table 3). Proteinuria measures were present in 230 081 (75%) women during the first trimester, with proteinuria detected in 6431 (2.8%). There was no association of first trimester–detected proteinuria and VTE [RR 1.02 (95% CI 0.13–2.00)]. A total of 162 965 (53.2%) women had an eGFR measure within 20 weeks of their conception date, of whom 157 617 (96.7%) had an eGFR $\geq$90 mL/min/1.73 m^2. Among these women, proteinuria was detected in 4842 (3.1%) and this was associated with a higher VTE risk [RR 1.97 (95% CI 1.28–3.06)]. Lastly, the association persisted in women with a diagnosis of diabetes or hypertension [diabetes RR 2.37 (95% CI 1.01–5.58), hypertension RR 3.16 (95% CI 1.42–7.05)].

DISCUSSION

This population-based retrospective cohort study examined the association of proteinuria and VTE risk in 306 244 pregnant women with deliveries and identified a number of key findings. Compared with its absence, proteinuria confers a significantly higher risk of VTE that remains consistent when examining a more specific definition. A higher VTE risk was noted with proteinuria in the post-partum period, in women with normal kidney function and among high-risk groups (diagnosed with diabetes or hypertension).

To our knowledge, this is the first study reporting the association of proteinuria and VTE in pregnancy. Proteinuria is a well-established risk factor for higher VTE risk in non-pregnant individuals. Massicotte-Azarniouch *et al.* [9] reported an independent association of proteinuria and VTE in 694 956 non-

Table 2. IPT-weighted RR of proteinuria and VTE

	VTE events, *n*	Deliveries, *n*	Crude percent	Crude risk per 10 000 person-years	Risk difference per 10 000 person-years (95% CI)	RR (95% CI)
VTE[a]						
Proteinuria[c]	32	8508	0.38	35.51	15.74 (3.04–28.44)	1.79 (1.25–2.57)
No proteinuria[d]	593	297 734	0.20	18.67	19.98 (18.38–21.59)	
VTE: sensitivity analysis[b]						
Proteinuria[c]	7	8508	0.09	7.76	6.18 (−0.19–12.54)	3.73 (1.70–8.21)
No proteinuria[d]	67	297 734	0.02	2.11	2.26 (1.72–2.80)	

[a]VTE defined by VTE code in the CIHI DAD or CIHI National Ambulatory Care Reporting System (NACRS).
[b]VTE sensitivity analysis: VTE code in CIHI DAD, CIHI NACRS or the Ontario Health Insurance Program (OHIP) and an imaging code within the CIHI DAD hospital admission or 7 days from an OHIP billing code or CIHI NACRS discharge date.
[c]Proteinuria: Aalbumin:creatinine ratio $\geq$3 mg/mmol using the first outpatient laboratory measurement within 20 weeks of the estimated conception date.
[d]No proteinuria: albumin:creatinine ratio <3 mg/mmol using the first outpatient laboratory measurement within 20 weeks of the estimated conception date.

Table 3. IPT-weighted RR of proteinuria and VTE in additional analyses

	VTE events, *n*	Deliveries, *n*	Crude percent	RR (95% CI)
Pre-partum[a]				
Proteinuria[b]	10	8510	0.12	1.26 (0.65–2.33)
No proteinuria[c]	257	297 734	0.09	
Post-partum[d]				
Proteinuria[b]	22	8510	0.26	2.21 (1.43–3.44)
No proteinuria[c]	336	297 734	0.11	
Proteinuria measure within first trimester				
Proteinuria[b]	25	8510	0.39	1.02 (0.13–2.00)
No proteinuria[c]	447	297 734	0.20	
Normal eGFR				
Proteinuria[b]	22	4842	0.45	1.97 (1.28–3.06)
No proteinuria[c]	341	152 775	0.22	
History of diabetes mellitus or gestational diabetes				
Proteinuria[b]	≤6[e]	793	0.76	2.37 (1.01–5.58)
No proteinuria[c]	51	16 067	0.32	
History of hypertension or gestational hypertension				
Proteinuria[b]	7	654	1.07	3.16 (1.42–7.05)
No proteinuria[c]	39	12 487	0.31	

[a]Pre-partum period: time from the date of estimated conception to delivery, where the day prior to the admission date is the end of the period.
[b]Proteinuria: albumin:creatinine ratio ≥3 mg/mmol using the first outpatient laboratory measurement within 20 weeks of the estimated conception date.
[c]No proteinuria: albumin:creatinine ratio <3 mg/mmol using the first outpatient laboratory measurement within 20 weeks of the estimated conception date.
[d]Post-partum period: time from the delivery admission to 6 months.
[e]In accordance with ICES privacy policies, cell sizes ≤5 cannot be reported.

pregnant individuals with a total of 15 180 VTE events. Consistent with this study, they found a high RR of VTE with proteinuria (>300 mg/day) in patients with normal kidney function [eGFR ≥90 mL/min/1.73 m^2, adjusted hazard ratio 1.61 (95% CI 1.38–1.89)]. A meta-analysis by Mahmoodi *et al.* [8] of 95 194 patients reported a step-wise increase in the RR of VTE with higher levels of proteinuria. The presence or detection of any degree of proteinuria, even relatively small amounts (>3 mg/mmol albumin:creatinine ratio or >5 mg/mmol protein:creatinine ratio), was associated with a significantly higher VTE risk [9].

A number of plausible mechanisms may contribute to a higher VTE risk with proteinuria. Proposed direct mechanisms include generalized endothelial disruption, inflammation and activation; loss of key components in the coagulation pathway; and intravascular volume depletion/stasis and oedema [11, 22, 23]. Indirectly, proteinuria may occur in conjunction with and exacerbate underlying medical conditions that heighten VTE risk, such as kidney disease, the hypertension–pre-eclampsia spectrum and thrombophilias [11]. In this study we attempted to isolate the presence of proteinuria by controlling for accompanying comorbid conditions and restricting the study cohort to women with normal kidney function.

Proteinuria testing is routinely and widely available, inexpensive and non-invasive, allowing for incorporation into clinical protocols for maternal health. Based on our findings, any measure of proteinuria, even in relatively low amounts, should alert healthcare providers to a heightened VTE risk. Furthermore, proteinuria should alert clinicians to adequate monitoring, suitable investigations for underlying causes and consideration of exacerbating risk factors (such as thrombophilia) [24]. As proteinuria is also an independent risk factor for haemorrhage, careful consideration of anticoagulation strategies is required [25].

We acknowledge our study has limitations. Proteinuria measures were not available in a considerable number of cases. Our administrative databases capture urine testing in laboratory settings and may not include urine dipstick tests in the office setting. It is conceivable a selection bias occurred, as sicker patients with high-risk pregnancies were more likely to undergo laboratory-based proteinuria testing. Deliveries by midwives that were not performed in a hospital may not be captured. Outcome misclassification of VTE in administrative databases has been reported [26]. We attempted to overcome this by using a combination of a validated (non-pregnancy cohort) high-specificity/high-likelihood definition of VTE (that likely underestimates the true number of VTE events) and a more broad high-sensitivity definition of VTE (that likely includes false positives) [17]. The consistency of the VTE–proteinuria association across both definitions strengthens our findings; however, our VTE definitions have not been validated in pregnancy *per se*. The observational nature of our study means that causality cannot be established. We were unable to account for potential unmeasured confounders such as thrombophilias, blood pressure measurements, antiplatelet agent use and oedema. Despite our large cohort size and population-based data, pregnancy-associated VTE remains a relatively rare event, with a small number of events and wide 95% CIs in certain subgroups. With the limited number of events, we were unable to distinguish PE/DVT in the subgroups of interest. Lastly, fatal VTE/PE events may not have been captured, suggesting a possible underestimate of true risk.

Proteinuria prior to 20 weeks of pregnancy is associated with a higher subsequent VTE risk. The risk was elevated in the postpartum period and was consistent when examining an alternative VTE definition, in women with normal kidney function and in those with a diagnosis of diabetes and hypertension. As such, the detection of proteinuria has potential important

implications in determining VTE risk during pregnancy and should prompt heightened concern.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

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AUTHORS' CONTRIBUTIONS

All authors consented to publication. M.M.S. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. A.A., E.K., M.M.S. and S.B. were involved in the concept and design. All authors were involved in the acquisition, analysis or interpretation of data. A.A. and M.M.S. drafted the manuscript. All authors were responsible for critical revision of the manuscript for important intellectual content. E.K. and A.B.E. were responsible for the statistical analysis. S.B. provided administrative, technical or material support. A.A. and M.M.S. provided supervision.

CONFLICT OF INTEREST STATEMENT

M.M.S. received speaker fees from AstraZeneca unrealted to the study. G.L.G received grants from Pfizer, Bristol Myers Squibb and personal fees from Pfizer, Sanofi and Leo outside the submitted work. A.A. received a grant from AstraZeneca and personal fees from AstraZeneca and Otsuka outside the submitted work.

DATA AVAILABILITY STATEMENT

Data are not available.

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