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Association Between Blunted Glomerular Hyperfiltration in Pregnancy and Severe Maternal Morbidity—A Research Letter

Ziv Harel[1,2], Alison L. Park[2], and Joel G. Ray[2,3]

Abstract

Background: Glomerular hyperfiltration is one physiological adaptation to pregnancy, marked by a decline in serum creatinine (SCr) concentration by 16 weeks' gestation. It is not known whether blunted glomerular hyperfiltration leads to adverse maternal outcomes, including severe maternal morbidity (SMM).
Objective: To evaluate the association between blunted glomerular hyperfiltration and subsequent SMM or death.
Design: Population-based cohort study
Setting: Ontario, Canada, from 2008 to 2019.
Participants: Included were births among women who had ≥ 1 SCr measured as an outpatient within 10 weeks before conception ("preconception"), and again, at $11^{0/7}$ to $20^{6/7}$ weeks' gestation ("in-pregnancy"). Excluded were women who died before birth, who had end-stage renal disease or kidney transplantation before conception, or whose pre-pregnancy SCr was 125 μmol/L.
Exposure: Net glomerular hyperfiltration defined as the preconception minus the in-pregnancy SCr.
Measures: The primary study outcome was SMM or death arising from 23 weeks' gestation up to 42 days after the index birth.
Methods: Adjusted relative risks (aRRs) were calculated using Modified Poisson regression per 1-SD net blunting of glomerular hyperfiltration adjusting for important covariates.
Results: A total of 10,323 births met all inclusion criteria. The mean (SD) SCr was 61.7 (11.0) μmol/L preconception, 48.0 (9.2) μmol/L in-pregnancy, and the mean net difference 13.6 (8.2) μmol/L. Among these births, the adjusted RR of SMM or death from 23 weeks' gestation up to 42 days post-partum was 1.16 (95% confidence interval 1.14-1.30) per 1-SD (8.2 μmol/L) net blunting of glomerular hyperfiltration.
Limitations: As SCr assessment is not a routine part of pregnancy care, its measurement could have been for a specific health condition thereby imparting selection bias.
Conclusions: Blunted glomerular hyperfiltration in pregnancy may identify some women at higher risk of SMM. Further prospective research is needed about the implications of glomerular hyperfiltration in early pregnancy.

Abrégé

Contexte: L'hyperfiltration glomérulaire est une adaptation physiologique à la grossesse qui se caractérise par une baisse du taux de créatinine sérique (CrS) à 16 semaines de gestation. On ignore toutefois si l'hyperfiltration glomérulaire atténuée entraîne des résultats indésirables pour la mère, notamment des cas graves de morbidité maternelle (morbidité maternelle grave—MMG).
Objectif: Examiner le lien entre l'hyperfiltration glomérulaire atténuée et une MMG subséquente ou le décès.
Type d'étude: Étude de cohorte basée sur une population.
Cadre: Étude menée en Ontario (Canada) entre 2008 et 2019.
Sujets: Ont été retenues pour l'étude les naissances liées à des femmes qui disposaient d'au moins une mesure de la CrS en consultation externe dans les 10 semaines précédant la conception («préconception») et d'une autre entre les semaines $11^{0/7}$ et $20^{6/7}$ de la grossesse («pendant la grossesse»). Ont été exclues les femmes décédées avant l'accouchement, celles qui étaient atteintes d'insuffisance rénale terminale ou qui avaient subi une transplantation rénale avant la conception, ainsi que celles qui présentaient une mesure de la créatinine sérique supérieure à 125 μmol/L avant la grossesse.
Exposition: La valeur de l'hyperfiltration glomérulaire nette a été définie comme la différence entre la mesure de CrS préconception et celle mesurée pendant la grossesse.

Mesures: Le principal critère d'évaluation était une MMG ou le décès dans la période couvrant de la 23e semaine de grossesse jusqu'à 42 jours après l'accouchement.
Méthodologie: Les risques relatifs corrigés (RRc) ont été calculés à l'aide d'un modèle de régression de Poisson modifié pour 1-ÉT pour l'hyperfiltration glomérulaire atténuée corrigée en tenant compte des covariables importantes.
Résultats: Au total, 10 323 naissances répondaient à tous les critères d'inclusion. Le taux de créatinine sérique moyen (ÉT) était de 61,7 (11,0) μmol/L préconception et de 48,0 (9,2) μmol/L pendant la grossesse. La différence nette moyenne s'établissait à 13,6 (8,2) μmol/L. Le RRc de MMG ou de décès pendant la période couvrant de la 23e semaine de grossesse jusqu'à 42 jours après l'accouchement s'établissait à 1,16 (IC 95 %: 1,14-1,30) pour 1-ÉT (8,2 μmol/L) d'hyperfiltration glomérulaire atténuée.
Limites: La mesure de la CrS n'étant pas une composante courante des soins liés au suivi d'une grossesse, les mesures disponibles pourraient avoir été faites dans un cadre spécifique, ce qui entraîne un biais de sélection.
Conclusion: L'hyperfiltration glomérulaire atténuée pendant la grossesse pourrait permettre de détecter les femmes qui présentent un risque accru de MMG. D'autres recherches prospectives portant sur les conséquences de l'hyperfiltration glomérulaire au début de la grossesse sont nécessaires.

Keywords
glomerular hyperfiltration, pregnancy, severe maternal morbidity

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Introduction

Glomerular hyperfiltration is one physiological adaptation to pregnancy, marked by a decline in serum creatinine (SCr) concentration by 16 weeks' gestation.[1] Glomerular hyperfiltration may be abnormally blunted in women with impaired renal vasculature, decreased nephron mass or pre-existing chronic kidney injury. Such blunting may heighten a woman's susceptibility to preeclampsia and acute kidney injury—both established causes of maternal morbidity.[2-4] Data are lacking on the effect of blunted glomerular hyperfiltration on the risk of severe maternal morbidity (SMM), especially among women without known antecedent kidney disease. The current study evaluated the association between blunted glomerular hyperfiltration and subsequent SMM or death.

Methods

We completed a retrospective population-based cohort study in Ontario, Canada, where universal health care is available. All hospital birth records were identified in administrative health databases, along with sociodemographic data and physician billing claims. These data sets were linked using unique encoded identifiers and analyzed at ICES.[1,4]

The cohort comprised women aged 16 to 50 years, who had a singleton livebirth or stillbirth at ≥23 weeks' gestation, from August 2008 to October 2019. Each participant had ≥1 SCr measured as an outpatient within 10 weeks before conception ("preconception"), and again, at $11^{0/7}$ to $20^{6/7}$ weeks' gestation ("in-pregnancy"). Excluded were women who died before birth, who had end-stage renal disease or kidney transplantation before conception, or whose pre-pregnancy SCr was >125 μmol/L as more severe kidney disease may be associated with morbidity measures that comprise SMM.[1]

Net glomerular hyperfiltration was determined by the preconception minus the in-pregnancy SCr. The primary study outcome was SMM or death arising from 23 weeks' gestation up to 42 days after the index birth. SMM is based on a validated composite measure comprising approximately 40 morbidity measures arising in pregnancy, during labor, or postpartum.[5] SMM or maternal death was further analyzed from the index birth up to 42 days postpartum.

Modified Poisson regression generated unadjusted and adjusted relative risks (RR) and 95% confidence interval (CI), modeled per 1-SD net blunting of glomerular hyperfiltration. One additional analysis was limited to women who had urinary protein measured ≤4 years before conception, with proteinuria further added to the regression model. Another analysis explored specific SMM components plausibly affected by impaired hyperfiltration, namely, severe preeclampsia, HELLP syndrome (characterized by hemolysis, elevated liver enzyme levels, and a low platelet count) or eclampsia; acute kidney injury or dialysis; and maternal ICU admission.[4,5]

Analyses were performed using SAS version 9.4 (SAS Institute), with a 2-sided P value $< .05$ for significance.

[1]Division of Nephrology, St. Michael's Hospital, Toronto, ON, Canada
[2]ICES, Toronto, ON, Canada
[3]Departments of Medicine and Obstetrics and Gynaecology, St. Michael's Hospital, Toronto, ON, Canada

Corresponding Author:
Ziv Harel, Division of Nephrology, St. Michael's Hospital, 61 Queen Street, Suite 730, Toronto, ON M5C 2T2, Canada.
Email: ziv.harel@unityhealth.to

Table 1. Risk of Severe Maternal Morbidity (SMM) or Death, or Specific SMM Components, Each in Association With a Blunting of Glomerular Hyperfiltration in Pregnancy.

Timing of assessment of outcome	Outcome	No. (overall %) with SMM or death	Unadjusted relative risk (95% CI)	Adjusted relative risk (95% CI)[a]	Adjusted relative risk with proteinuria (95% CI)[b]
23 weeks' gestation up to 42 days postpartum	SMM or death	354 (3.43)	1.14 (1.03-1.27)	1.16 (1.04-1.30)	1.20 (1.07-1.36)
	Severe preeclampsia, HELLP syndrome or eclampsia	97 (0.94)	1.18 (0.93-1.51)	1.27 (1.01-1.60)	1.34 (1.03-1.74)
	Acute kidney injury or dialysis	21 (0.20)	1.10 (0.61-2.00)	1.44 (1.02-2.04)	1.57 (1.18-2.10)
	Maternal ICU admission	59 (0.57)	1.13 (0.89-1.45)	0.90 (0.66-1.23)	0.94 (0.68-1.31)
Index birth up to 42 days postpartum	SMM or death	183 (1.77)	1.02 (0.89-1.18)	0.97 (0.83-1.14)	1.03 (0.87-1.21)

Note. Each outcome is expressed per 1-SD (8.2 μmol/L) blunting of the serum creatinine between the preconception and in-pregnancy periods.
CI = confidence interval; ICU = intensive care unit.
[a]Adjusted for maternal age, rural residence, income quintile (each at time of index conception); gestational week of in-pregnancy serum creatinine; preconception serum creatinine; and diabetes mellitus, chronic hypertension, and tobacco/illicit drug—each within 4 years before conception.
[b]Further limited to 6992 pregnancies with a urine albumin-creatinine ratio or dipstick measurement done within 4 years before conception, and adjusted for proteinuria (defined as a urine albumin-creatinine ratio > 2 mg/mmol or a urine dipstick positive for protein).

Results

A total of 10,323 births met all inclusion criteria. The mean (SD) SCr was 61.7 (11.0) μmol/L preconception, 48.0 (9.2) μmol/L in-pregnancy, and the mean net difference 13.6 (8.2) μmol/L.

Among 10,323 births, the adjusted RR of SMM or death from 23 weeks' gestation up to 42 days post-partum was 1.16 (95% CI 1.14-1.30) per 1-SD (8.2 μmol/L) net blunting of glomerular hyperfiltration, which changed minimally after adjusting for a history proteinuria (Table 1). The associated risk was higher for severe preeclampsia, and for acute kidney injury or dialysis, but not for maternal ICU admission (Table 1).

A net blunting of glomerular hyperfiltation was not associated with SMM or death arising from birth to 42 days postpartum (Table 1).

Discussion

These preliminary findings suggest that blunted glomerular hyperfiltration in pregnancy may identify some women at higher risk of SMM.

This study has some limitations. First, as SCr assessment is not a routine part of pregnancy care, its measurement herein could have been for a specific health condition. Second, due to data limitations, we did not account for all important confounders which may affect SCr and the ability to hyperfilter, including body mass index and previous episodes of hypertensive disorders of pregnancy. While the ensuing selection bias may have included women especially at higher risk of SMM, these would also represent women who might benefit from enhanced surveillance and preventive strategies. One example might be aspirin prophylaxis, which decreases the risk of preeclampsia, one major cause of SMM.[6]

Further prospective research is needed about the implications of glomerular hyperfiltration in early pregnancy.

Ethics Approval and Consent to Participate

The use of the data was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a Research Ethics Board.

Consent for Publication

We consent to publish this paper.

Availability of Data and Materials

The data set from this study is held securely in coded form at ICES. Although data-sharing agreements prohibit ICES from making the data set publicly available, access may be granted to those who meet prespecified criteria for confidential access, available at www.ices.on.ca/DAS. The full data set, creation plan and underlying analytic code are available from the authors upon request, with the understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

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Author Contributions

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Declaration of Conflicting Interests

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ORCID iD

Ziv Harel https://orcid.org/0000-0002-8618-4538

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