High potassium level during pregnancy is associated with future cardiovascular morbidity

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Abstract

Objective: The present study was aimed to determine whether high potassium level during pregnancy is an independent risk factor for future atherosclerotic morbidity.

Patients and methods: A case–control study was conducted including women who delivered between the years 2000–2012 and subsequently developed atherosclerotic morbidity after their last delivery (n = 653) and matched controls (n = 4101). The mean follow-up duration was 57.7 ± 36.5 and 78.5 ± 42.3 months, respectively. The cases were further divided into: major events (severe atherosclerotic morbidity; n = 363), minor events (i.e. cardiovascular risk factors; n = 201) and cardiovascular evaluation tests (n = 89). The Cox proportional hazards models were used to estimate the adjusted hazard ratios (HR) for hospitalizations while controlling for confounders.

Results: A Cox proportional hazard model, controlling for confounders such as gestational hypertension, gestational diabetes mellitus, obesity, maternal age, creatinine level and gestational week at index pregnancy showed that K+ ≥ 5.0 mEq/L during pregnancy was significantly associated with hospitalizations due to severe atherosclerotic morbidity (adjusted HR = 1.55; 95% CI 1.02–2.35; p = 0.039). A non-significant trend was also noted with long-term total hospitalizations for atherosclerotic (adjusted HR = 1.39; 95% CI 0.99–1.94; p = 0.052).

Conclusion: High potassium level during pregnancy is associated with a significant risk for severe atherosclerotic morbidity, as it might be an indication for occult metabolic and renal dysfunction.

Keywords
Cardiovascular, potassium, pregnancy

Introduction

The normal level of plasma potassium during pregnancy is not defined. Through pregnancy there are opposite forces that influence the plasma potassium level. On one hand, there is elevated plasma aldosterone, which favors potassium urinary excretion. On the other hand, the elevated progesterone which is mineralocorticoid receptor blocker, functions as aldosterone antagonist [1]. Although pregnant women preserve about 350 mEq potassium, it is mostly stored as intracellular ion [2].

Previously, our group showed that high potassium level during the first half of pregnancy is associated with higher risk for the development of gestational diabetes mellitus (GDM) and severe preeclampsia [3]. On the contrary, hypokalemia in non-pregnant women is linked to metabolic syndrome [4,5].

For the past several years, there are growing number of publications showing the association between pregnancy complications such as gestational hypertension and GDM and long-term maternal atherosclerotic morbidity [6–8]. This notion received further confirmation by the guidelines published at 2011 emphasizing the importance of history of pregnancy complications in cardiovascular risk stratification [9].

The present study was aimed to determine whether high potassium level during pregnancy might be a risk factor for future atherosclerotic morbidity.

Methods

The study was performed in a case–control design. The study population included women who delivered between the years 2000–2012 at the Soroka University Medical Center (n = 169,059).

Cases

All women who gave birth at the Soroka University Medical Center and were subsequently hospitalized between the years 2000 and 2012 (in the non-pregnant period) with at least one
Obesity was defined as maternal pre-pregnancy body mass index (BMI) of 30 kg/m² or more according to the records (n = 5541). (1) Major events: Cardiovascular involvement, cerebrovascular disease, chronic renal failure, diabetic and hypertensive disease with target organ damage and/or acute complications (such as diabetic ketoacidosis, hyperosmolar state and hypertensive crisis). (2) Minor events: Atherosclerotic risk factors such as diabetes mellitus, essential hypertension and dyslipidemia without the above-mentioned complications and (3) Cardiac evaluation: This group was composed of women who underwent stress test, cardiac scan, cardiac coronary angiography without detection of coronary atherosclerosis during their hospitalization. The exact International Classification of Diseases, 9th edition (ICD-9) coding for each subtype of cardiovascular morbidity are presented in the Appendix (Supplementary Table S1).

Women with more than one hospitalization were classified to the more severe morbidity group (major events, minor events and cardiac evaluation).

Controls

Women who gave birth at the Soroka University Medical Center between the years 2000 and 2012 and were not subsequently hospitalized with the above diagnoses, in a non-pregnant period, between the years 2000 and 2012 were included. About four controls were matched to each one of the cases, according to their year of birth (n = 21 419).

Exclusion criteria

Multiple pregnancies and known cardiovascular and cerebrovascular disease as well as renal failure and atherosclerotic risk factors (hypertension, diabetes mellitus and hyperlipidemia) prior to the index pregnancy were excluded.

From the study population, we retrieved subjects who had at least one potassium (K⁺) measurement during their pregnancies. A comparison was performed between cases and controls. For each subject in the study population, the highest value of potassium during pregnancy was chosen, and this pregnancy was defined as the index pregnancy. Potassium level was divided into the following categories: K⁺ ≤ 3.5 mEq/L; K⁺ = 3.51–3.99 mEq/L, K⁺ = 4.0–4.99 mEq/L and K⁺ ≥ 5.0 mEq/L [3].

The diagnosis of GDM was made according to the criteria proposed by the Fourth International Workshop-Conference on gestational diabetes [7]. Gestational hypertension was diagnosed according to the task force on hypertension in pregnancy criteria [10].

Obesity was defined as maternal pre-pregnancy body mass index (BMI) of 30 kg/m² or more according to the records upon admission for labor.

The study received the approval of the ethics committee of our institute.

Statistical analysis

Statistical analysis was performed using the SPSS package 17 edition (SPSS Inc, Chicago, IL). Statistical significance was calculated using the chi-square test for differences in qualitative variables and the Student t-test for differences in continuous variables. Cox proportional hazards models were constructed in order to estimate the adjusted hazard ratios (HR) for hospitalizations while controlling for potential confounders.

Results

From the study sample of 26 960 women (5541 cases and 21 419 controls), 4754 women had at least one potassium measurement during their pregnancy [653 cases (hospitalized group) and 4101 (controls)]. The cases included 363 (56%) women who were hospitalized due to major events, 201 (31%) women due to minor events and 89 (13%) for cardiac evaluation.

In the major event group, the 363 women included 283 women with cardiovascular damage (involving heart, brain and large vessels) and 80 with severe complications of atherosclerotic risk factors including: renal involvement, diabetic ketoacidosis, hyperosmolar state and hypertensive crisis.

For the cases, the mean follow-up period between the index pregnancy and the hospitalization was 57.7 ± 36.5 months. The mean follow-up of the control group between the index pregnancy and the end of the study period (31.12.2012) was 78.5 ± 42.3.

General characteristics: cases versus controls

The basic characteristics of the study population at the index pregnancy are presented in Table 1. The cases had a significantly higher maternal age at the index pregnancy, higher birth-order, and higher rates of obesity, GDM, gestational hypertension and potassium level at their index pregnancy.

Potassium level at index pregnancy and risk for long-term maternal hospitalization

The prevalence of the lowest level of plasma potassium (K⁺ ≤ 3.5 mEq/L) was the highest in the control group compared with the all categories of cases, while the highest category of plasma potassium (K⁺ ≥ 5.0 mEq/L) was most prevalent among case with the hospitalization due to major event, gradually declining with severity (from 6.9% in the most severe morbidity group to 3.4% in the least severe morbidity group and controls); (p = 0.004 linear-by-linear association) (Figure 1).

Table 1. Clinical characteristics of cases and controls at the index pregnancy: mean ± standard deviation (SD) and rates (%).

|                          | Controls N = 4101 | Cases N = 653 |
|--------------------------|-------------------|---------------|
| Maternal age (years)     | 32.99 ± 6.48      | 34.48 ± 6.21  |
| Gravidity (mean ± SD)    | 4.55 ± 3.50       | 5.89 ± 3.88   |
| Parity (mean ± SD)       | 3.82 ± 2.95       | 4.86 ± 3.44   |
| Obesity N (%)            | 46 (1.2)          | 19 (2.9)      |
| Gestational diabetes mellitus N (%) | 545 (13.3) | 211 (32.3) |
| Pregnancy induced hypertension N (%) | 404 (12.9) | 84 (19.9) |
| Potassium at index pregnancy (mEq/dl) | 4.18 ± 0.40 | 4.30 ± 0.49 |
Potassium level during pregnancy is an independent risk factor for cardiovascular morbidity in non-pregnant life

In order to evaluate the role of potassium level during pregnancy as a marker for later atherosclerotic morbidity, we performed multivariate analyses.

Cox regression models, controlling for: maternal age, GDM, gestational hypertension, creatinine level at index pregnancy and the gestational week of potassium measurement, were constructed. A non-significant association was noted between K⁺ ≥5.0 mEq/L and above and future total atherosclerotic hospitalizations (adjusted HR = 1.39 CI 0.99–1.94 p = 0.052; Table 2). However, when restricting the analysis to hospitalizations due to major events, K⁺ ≥5.0 mEq/L at index pregnancy was noted as an independent risk factor for long-term hospitalizations (adjusted HR = 1.55 CI 1.02–2.35 p = 0.039; Table 3).

Discussion

Plasma potassium level of 5 mEq/L and above was independently associated with increased future hospitalization due to major atherosclerotic morbidity, including cardiovascular damage and severe complications of atherosclerotic risk factors (renal failure, hypertensive crisis, hyperosmolar state and diabetic ketoacidosis). Potassium level was preserved as independent risk even after controlling for creatinine level. This might suggest that potassium is a marker for metabolic and vascular alteration during pregnancy. Previously, our group demonstrated that relatively high potassium level at the first half of pregnancy was associated with the development of pregnancy metabolic complications such as GDM and preeclampsia during the second half of pregnancy [3]. We suggested that low plasma potassium during pregnancy might reflect an appropriate increase in GFR and insulin secretion.

Despite the net increase in body stores of sodium and potassium, serum levels of both electrolytes decrease during pregnancy by 4 and 0.25 mEq/L, respectively [11]. Actually, normal potassium during pregnancy can reach the level of 3.25 mEq/L [12]. This reduction in plasma potassium level is probably due to renal and metabolic adaptation to normal pregnancy. Plasma potassium level is affected by urinary secretion and by its distribution between the intracellular and extracellular body fluid [13]. Insulin is one of the hormones that shifts potassium from extracellular to the intracellular fluid [14]. Increased insulin level during pregnancy [15] keeps the glucose in normal range, but also causes reduction in plasma potassium level. The decrease in plasma potassium level is also due to an increased urinary secretion of potassium which is mainly affected by an increased glomerular filtration rate [11]. The net result of all those changes is decreased plasma potassium level [12]. It might be suggested that elevated plasma potassium level during pregnancy is due to metabolic and renal malfunction.

Overt metabolic and vascular abnormalities during pregnancy such as GDM and gestational hypertension are strongly associated with long-term diabetes mellitus, chronic hypertension and cardiovascular morbidity [7,16,17]. However, other pregnancy complication such as stillbirth and placental abruption were also found to be associated with future atherosclerotic morbidity [18,19]. This variety of associations suggests that pregnancy abnormalities are not only due to placental abnormalities, but there might be primary maternal vascular-metabolic dysfunction that is revealed during pregnancy. In the current study, we demonstrated that potassium might serve as a surrogate marker for future atherosclerotic abnormalities.
In conclusion, pregnancy is a unique physiological condition that puts the woman in metabolic and vascular challenges. In some cases, the woman develops explicit complications such as GDM and gestational hypertension. However, in other cases the woman is asymptomatic and there are only laboratory abnormalities or variations that hint about the metabolic and vascular dysfunction. These women might be at an increased risk for long-term atherosclerotic morbidity and should be advised for an earlier control of traditional risk factors.

Declaration of interest
The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

References
1. Couette B, Lombes M, Baulieu EE, Rafestin-Oblin ME. Aldosterone antagonists destabilize the mineralocorticosteroid receptor. Biochem J 1992;282:697–702.
2. Lindheimer MD, Richardson DA, Ehrlich EN, Katz AI. Potassium homeostasis in pregnancy. J Reprod Med 1987;32:517–22.
3. Wolak T, Sergienko R, Wiznitzer A, et al. Low potassium level during the first half of pregnancy is associated with lower risk for the development of gestational diabetes mellitus and severe pre-eclampsia. J Matern Fetal Neonatal Med 2010;23:994–8.
4. Sun K, Su T, Li M, et al. Serum potassium level is associated with metabolic syndrome: a population-based study. Clin Nutr 2014;33:521–7.
5. Reungjui S, Pratipanawatr T, Johnson RJ, Nakagawa T. Do thiazides worsen metabolic syndrome and renal disease? The pivotal roles for hyperuricemia and hypokalemia. Curr Opin Nephrol Hypertens 2008;17:470–6.
6. Callaway LK, Lawlor DA, O’Callaghan M, et al. Diabetes mellitus in the 21 years after a pregnancy that was complicated by hypertension: findings from a prospective cohort study. Am J Obstet Gynecol 2007;197:492 e1–7.
7. Shalom G, Shoham-Vardi I, Sergienko R, et al. Is preeclampsia a significant risk factor for long-term hospitalizations and morbidity? J Matern Fetal Neonatal Med 2013;26:13–15.
8. Fraser A, Nelson SM, Macdonald-Wallis C, et al. Associations of pregnancy complications with calculated cardiovascular disease risk and cardiovascular risk factors in middle age: the Avon Longitudinal Study of Parents and Children. Circulation 2012;125:1367–80.
9. Mosca L, Benjamin EJ, Berra K, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women – 2011 update: a guideline from the American heart association. Circulation 2011;123:1243–62.
10. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists’ Task Force on Hypertension in Pregnancy. Obstet Gynecol 2013;122:1122–31.
11. Odutayo A, Hladunewich M. Obstetric nephrology: renal hemodynamic and metabolic physiology in normal pregnancy. Clin J Am Soc Nephrol 2012;7:2073–80.
12. Larsson A, Palm M, Hansson LO, Axelsson O. Reference values for clinical chemistry tests during normal pregnancy. BJOG 2008;115:874–81.
13. Kamel KS, Schreiber M, Halperin ML. Integration of the response to a dietary potassium load: a paleolithic perspective. Nephrol Dial Transplant 2014;29:982–9.
14. Al-Khalili L, Yu M, Chibalin AV. Na+-K+-ATPase trafficking in skeletal muscle: insulin stimulates translocation of both alpha 1- and alpha 2-subunit isoforms. FEBS Lett 2003;536:198–202.
15. Parsons JA, Breijte TC, Sorenson RL. Adaptation of islets of Langerhans to pregnancy: increased islet cell proliferation and insulin secretion correlates with the onset of placental lactogen secretion. Endocrinology 1992;130:1459–66.
16. Harreiter J, Dovjak G, Kautzky-Willer A. Gestational diabetes mellitus and cardiovascular risk after pregnancy. Womens Health (Lond Engl) 2014;10:91–108.
17. Kessous R, Shoham-Vardi I, Pariente G, et al. An association between preterm delivery and long-term maternal cardiovascular morbidity. Am J Obstet Gynecol 2013;209:368 e1–8.
18. Pariente G, Shoham-Vardi I, Kessous R, et al. Is stillbirth associated with long-term atherosclerotic morbidity? Am J Obstet Gynecol 2014;211:416.e1–12.
19. Pariente G, Shoham-Vardi I, Kessous R, et al. Placental abruption as a significant risk factor for long-term cardiovascular mortality in a follow-up period of more than a decade. Paediatr Perinat Epidemiol 2014;28:32–8.

Supplementary material available online