Renin Angiotensin Aldosterone System and Glycemia in Pregnancy

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SUMMARY

Background: The renin-angiotensin-aldosterone system (RAAS) is involved in the pathogenesis of insulin resistance and type 2 diabetes in the general population. The RAAS is activated during pregnancy. However, it is unknown whether the RAAS contributes to glycemia in pregnant women.

Methods: Plasma renin activity (PRA) and plasma aldosterone levels were quantified at delivery in 689 Chinese mothers. An oral glucose tolerance test in fasted women was performed in the second trimester of pregnancy. The diagnosis of gestational diabetes mellitus (GDM) and impaired glucose tolerance during pregnancy were made according to the guidelines of the Chinese Society of Obstetrics.

Results: Plasma aldosterone was significantly higher in pregnant women with GDM as compared to those without impairment of glycemic control (normal pregnancies: 0.27 ±0.21 ng/mL, GDM: 0.36 ±0.30 ng/mL; p<0.05). Regression analyses revealed that PRA was negatively correlated with fasting blood glucose (FBG) (R² = 0.03, p = 0.007), whereas plasma aldosterone and aldosterone/PRA ratio were positively correlated with FBG (R² = 0.05, p<0.001 and R² = 0.03, p = 0.007, respectively). Multivariable regression analysis models considering relevant confounding factors confirmed these findings.

Conclusions: This study demonstrated that fasting blood glucose in pregnant women is inversely correlated with the PRA, whereas plasma aldosterone showed a highly significant positive correlation with fasting blood glucose during pregnancy. Moreover, plasma aldosterone is significantly higher in pregnant women with GDM as compared to those women with normal glucose tolerance during pregnancy. Although causality cannot be proven in association studies, these data may indicate that the RAAS during pregnancy contributes to the pathogenesis of insulin resistance/new onset of diabetes during pregnancy.

KEY WORDS

Renin-angiotensin-aldosterone system, pregnancy, fasting blood glucose, glycemic control

INTRODUCTION

GDM is a condition in which pregnant women without previously diagnosed diabetes have high FBG and an impaired response to glucose load. The prevalence of GDM in different countries is 1 - 14% depending on ethnicity and diagnosis standard [1,2]. No specific cause has been identified, but it is believed that in particular sex hormones produced during pregnancy increases a woman's resistance to insulin, resulting in impaired glucose tolerance [3,4]. In humans, the RAAS undergoes major changes in response to pregnancy. There is an
early increase in renin due to local release by the ovaries and maternal decidua. Angiotensinogen synthesis by the liver is increased by circulating estrogen produced by the growing placenta. This leads to increased serum angiotensin II and aldosterone levels [5]. An activated RAAS has been implicated in the pathogenesis of insulin resistance and type 2 diabetes. Patients on antihypertensive treatment with drugs affecting the RAAS such as angiotensin converting enzyme (ACE) inhibitors and angiotensin (AT1) receptor blockers have a lower incidence of new onset diabetes and show improved insulin sensitivity [6-10]. From animal models it is known that the application of AT1 receptor blockers improves glucose tolerance through enhancement of insulin-mediated glucose uptake in peripheral organs like skeletal muscle, possibly due to changes in blood flow [11]. Also, changes in muscle fiber composition, decreased concentrations of tumour necrosis factor-alpha in skeletal muscle and cross-talk in the signaling pathways of angiotensin and insulin receptors are discussed as an explanation of the observed phenomena [11,12].

So far, it is unknown whether the activity of the RAAS during pregnancy is linked to insulin resistance or onset of diabetes as it is known in the general population. The aim of our study was to analyze the relationship of key parameters of the RAAS in pregnant women and glyce mia during pregnancy.

**MATERIALS AND METHODS**

**Clinic data collection**

The study was approved by the ethics committee of Jinan University, Guangzhou, China. We invited a total of 810 Chinese women who delivered their babies at the Obstetric Department of the First Affiliated Hospital of Jinan University between March 2010 and October 2010 to participate in the study. Inclusion criteria were as follows: (1) the newborn was born without structural anomalies; (2) singleton pregnancy; (3) no HIV or major medical illness; (4) no drug or heavy alcohol abuse. After exclusion of cases that did not fulfill the inclusion criteria or who were not willing to participate, we finally included 689 remaining cases. After obtaining written consent, a structured medical history was taken. Chinese guidelines for medical follow-up in pregnancy includes a ‘Perinatal health manual’ which contains essential data about the pregnancy. The data in the ‘Perinatal health manual’ were also used to judge whether the women fulfilled all inclusion and exclusion criteria. The following data were extracted into our database: nationality, age, height, body height, body weight before and during pregnancy, gravidity, parity, gestational age at delivery, smoking before/during pregnancy, alcohol during pregnancy, and blood pressure readings at all follow-up visits.

Gestational age was based on the first day of the last normal menstrual period and confirmed by either first or early second trimester ultrasound scans. Biometric data of the newborns were routinely measured immediately after delivery. Measurement of PRA, aldosterone, and an oral glucose tolerance test was done in all participating pregnant women.

The criteria for diagnosis of preeclampsia is as follows: showing a systolic blood pressure of ≥140 mm Hg and/or a diastolic blood pressure of ≥90 mm Hg, taken over a period of 4 to 6 hours after 20 weeks gestation, and urinary total protein of ≥300 mg in 24 hours or urine dipstick indicating ≥1+ of protein [13]. According to Chinese guidelines [14], plasma glucose concentrations were measured at 0, 60, and 120 minutes after a 12-hour fasting period. For this glucose tolerance test, the woman received at 75-g oral glucose load in the second trimester of pregnancy, screening for GDM. GDM was diagnosed when patient plasma glucose levels exceeded two of the following thresholds: fasting glucose ≥5.6 mmol/L; one hour glucose ≥10.3 mmol/L or two hour glucose ≥8.6 mmol/L. Impaired glucose tolerance during pregnancy was diagnosed when patient glucose levels exceeded one of the above mentioned criteria.

**Biochemical analysis**

Midwives collected maternal blood from a cubital vein in the delivery room or on the ward before delivery. The maternal blood was infused into the special anticoagulant tube, which included 0.3M EDTA, 0.32 M dimer caprol and 0.34 M 8-hydroxyquinoline sulfate, for the PRA measurement and into a lithium tube for measurement of plasma aldosterone levels. All the samples were separated immediately into aliquots of plasma and blood cells for storage at -20°C until analysis. PRA and plasma aldosterone were measured by radioimmunoassay (Beijing North Institute of Biological Technology, Beijing, China, CAT number: D01PZB for PRA measurements (angiotensin I RIA), D03PZB for aldosterone measurements) on a GC-1200 radioimmunoassay counter (Anhui ustc zonkia scientific instruments co., LTD, China). Plasma renin activity was measured by analyzing the generation of angiotensin I. Angiotensin I concentrations were detected by RIA (D01PZB). We have chosen the measurement of plasma renin activity instead of simple renin concentration, because this method is the most widely accepted reference method to describe renin in clinical science. All the blood samples were measured by experienced technologists in a certified laboratory of the hospital.

**Data analysis**

Data were analyzed with SPSS version 17.0. Results are presented as mean ± standard deviation (SD). Students’ unpaired t-test was used for comparison of continuous variables between groups. Multivariable regression analysis was used to adjust for confounding variables known to independently influence insulin resistance during pregnancy like maternal age and BMI before pregnancy. A p-value of less than 0.05 was considered significant.
Table 1. Detailed Descriptive Data (n = 689).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age, years</td>
<td>28.5 ±3.7</td>
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<tr>
<td>Gravidity, %</td>
<td>1.77 ±1.09</td>
</tr>
<tr>
<td>Parity, %</td>
<td>1.19 ±0.44</td>
</tr>
<tr>
<td>History of hypertension, %</td>
<td>0.4</td>
</tr>
<tr>
<td>Preeclampsia during pregnancy, %</td>
<td>3.05</td>
</tr>
<tr>
<td>Diabetes mellitus during pregnancy, %</td>
<td>9.1</td>
</tr>
<tr>
<td>Impaired glucose tolerance during pregnancy, %</td>
<td>15.2</td>
</tr>
<tr>
<td>Smoking before/during pregnancy, %</td>
<td>0.44/0.15</td>
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<tr>
<td>Alcohol during pregnancy, %</td>
<td>0.15</td>
</tr>
<tr>
<td>Maternal height, cm</td>
<td>159.91 ±4.52</td>
</tr>
<tr>
<td>BMI (Body mass index) before pregnancy, kg/m²</td>
<td>20.2 ±2.46</td>
</tr>
<tr>
<td>Maternal weight before pregnancy, kg</td>
<td>51.71 ±6.9</td>
</tr>
<tr>
<td>Maternal weight at delivery, kg</td>
<td>67.71 ±8.2</td>
</tr>
<tr>
<td>Child birth weight, g</td>
<td>3269.3 ±427.7</td>
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<tr>
<td>Gestational age at delivery, day</td>
<td>274.7 ±9.3</td>
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<tr>
<td>Child gender, male/female, %</td>
<td>54.6/45.4</td>
</tr>
<tr>
<td>Apgar score at 1 min</td>
<td>8.91 ±0.54</td>
</tr>
<tr>
<td>Apgar score at 5 min</td>
<td>9.96 ±0.23</td>
</tr>
<tr>
<td>Apgar score at 10 min</td>
<td>9.99 ±0.09</td>
</tr>
<tr>
<td>Maternal PRA, ng/mL/h</td>
<td>5.87 ±3.977</td>
</tr>
<tr>
<td>Maternal plasma aldosterone, ng/mL</td>
<td>0.28 ±0.23</td>
</tr>
<tr>
<td>Maternal aldosterone/PRA ratio</td>
<td>0.28 ±0.97</td>
</tr>
<tr>
<td>Oral glucose tolerance test time, day</td>
<td>187.2 ±18.4</td>
</tr>
<tr>
<td>FBG, mmol/L</td>
<td>4.75 ±0.63</td>
</tr>
<tr>
<td>Blood glucose concentration, one hour, mmol/L</td>
<td>8.76 ±1.83</td>
</tr>
<tr>
<td>Blood glucose concentration, two hour, mmol/L</td>
<td>7.46 ±1.47</td>
</tr>
</tbody>
</table>

Data are given as mean ± SD or %. FBG: fasting blood glucose, PRA: plasma renin activity.

RESULTS

Description of the cohort
The demographic data of the cohort is presented in Table 1. The mean maternal PRA was 5.87 ±3.977 ng/mL/h. The mean maternal plasma aldosterone was 0.28 ±0.23 ng/mL. The mean maternal aldosterone/PRA ratio was 0.28 ±0.97 (for details see Table 1). Regression analysis showed that PRA was negatively correlated with plasma aldosterone (R² = 0.139, p<0.001), which fits with a feed-back suppression of renal renin release [15-17]. PRA was significantly higher in normotensive pregnancies as compared to preeclampsia pregnancies (normotensive pregnancies: 6.03 ±3.97 ng/mL/h, preeclampsia pregnancy: 2.13 ±1.48 ng/mL/h; p<0.01), plasma aldosterone was not significantly different in those two groups (0.28 ±0.23 ng/mL and 0.25 ±0.23 ng/mL, respectively, p = 0.56).

RAAS and glycemic control
Plasma aldosterone was significantly higher in pregnant women with GDM compared to those with normal glucose tolerance (normal glucose tolerance: 0.27 ±0.21 ng/mL, GDM: 0.36 ±0.30 ng/mL; p<0.05) (for details see Table 2). This finding was confirmed in a regression analysis. Plasma aldosterone and aldosterone/PRA ratios were positively correlated with FBG (R² = 0.05, p<0.001 and R² = 0.03, p = 0.007, respectively). In contrast PRA was negatively correlated with FBG (R² = 0.03, p = 0.007) (Figure 1).

The stability of the stated results were proved by adding maternal age, maternal BMI before pregnancy, oral glucose tolerance test time and the time for RAAS analysis as confounding factors to a multivariable regression model. The correlations between RAAS and FBG were confirmed in this model. When adding both PRA and
Table 2. RAAS in normal pregnancies, pregnancies with impaired glucose tolerance and gestational diabetes mellitus.

<table>
<thead>
<tr>
<th></th>
<th>Normal pregnancies (n = 521)</th>
<th>Impaired glucose tolerance (n = 105)</th>
<th>Gestational diabetes mellitus (n = 63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRA, ng/mL/h</td>
<td>5.97 ± 3.92</td>
<td>5.88 ± 4.29</td>
<td>5.07 ± 3.96</td>
</tr>
<tr>
<td>Aldosterone, ng/mL</td>
<td>0.27 ± 0.21</td>
<td>0.28 ± 0.27</td>
<td>0.36 ± 0.30</td>
</tr>
<tr>
<td>Aldosterone/PRA ratio</td>
<td>0.22 ± 0.65</td>
<td>0.42 ± 1.50</td>
<td>0.59 ± 1.78</td>
</tr>
</tbody>
</table>

Data are given as mean ± SD. #: p < 0.05 versus normal pregnancies, FBG: fasting blood glucose, PRA: plasma renin activity.

Table 3. Multivariable regression analyses of the association between different markers of the renin-angiotensin-system and fasting blood glucose (in mmol/L) as dependent variable.

<table>
<thead>
<tr>
<th>Model (R²) and independent variables</th>
<th>B</th>
<th>95% CI lower</th>
<th>95% CI upper</th>
<th>SE</th>
<th>T</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (0.06)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRA, ng/mL/h</td>
<td>-0.03</td>
<td>-0.05</td>
<td>-0.01</td>
<td>0.01</td>
<td>-2.78</td>
<td>0.006</td>
</tr>
<tr>
<td>Maternal age, years</td>
<td>0.02</td>
<td>0.01</td>
<td>0.04</td>
<td>0.01</td>
<td>1.16</td>
<td>0.246</td>
</tr>
<tr>
<td>Maternal BMI before pregnancy, kg/m²</td>
<td>0.03</td>
<td>-0.01</td>
<td>0.07</td>
<td>0.02</td>
<td>1.63</td>
<td>0.104</td>
</tr>
<tr>
<td>Oral glucose tolerance test time, day</td>
<td>&lt;0.01</td>
<td>-0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>-1.50</td>
<td>0.134</td>
</tr>
<tr>
<td>Gestational age at delivery, day</td>
<td>&lt;0.01</td>
<td>-0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>-0.26</td>
<td>0.794</td>
</tr>
<tr>
<td>B (0.067)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aldosterone, ng/mL</td>
<td>0.60</td>
<td>0.36</td>
<td>0.83</td>
<td>0.12</td>
<td>4.98</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Maternal age, years</td>
<td>0.01</td>
<td>-0.01</td>
<td>0.03</td>
<td>0.01</td>
<td>0.96</td>
<td>0.337</td>
</tr>
<tr>
<td>Maternal BMI before pregnancy, kg/m²</td>
<td>0.02</td>
<td>&lt;0.01</td>
<td>0.04</td>
<td>0.01</td>
<td>1.56</td>
<td>0.199</td>
</tr>
<tr>
<td>Oral glucose tolerance test time, day</td>
<td>&lt;0.01</td>
<td>-0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>-1.70</td>
<td>0.090</td>
</tr>
<tr>
<td>Gestational age at delivery, day</td>
<td>&lt;0.01</td>
<td>-0.01</td>
<td>0.01</td>
<td>&lt;0.01</td>
<td>0.17</td>
<td>0.868</td>
</tr>
<tr>
<td>C (0.062)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aldosterone/PRA ratio</td>
<td>0.12</td>
<td>0.04</td>
<td>0.21</td>
<td>0.04</td>
<td>2.93</td>
<td>0.004</td>
</tr>
<tr>
<td>Maternal age, years</td>
<td>0.01</td>
<td>-0.01</td>
<td>0.03</td>
<td>0.01</td>
<td>1.04</td>
<td>0.301</td>
</tr>
<tr>
<td>Maternal BMI before pregnancy, kg/m²</td>
<td>0.03</td>
<td>-0.01</td>
<td>0.06</td>
<td>0.02</td>
<td>1.30</td>
<td>0.194</td>
</tr>
<tr>
<td>Oral glucose tolerance test time, day</td>
<td>&lt;0.01</td>
<td>-0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>-1.80</td>
<td>0.074</td>
</tr>
<tr>
<td>Gestational age at delivery, day</td>
<td>&lt;0.01</td>
<td>-0.01</td>
<td>0.01</td>
<td>&lt;0.01</td>
<td>0.43</td>
<td>0.670</td>
</tr>
<tr>
<td>D (0.091)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aldosterone, ng/mL</td>
<td>0.49</td>
<td>0.18</td>
<td>0.80</td>
<td>0.16</td>
<td>3.09</td>
<td>0.002</td>
</tr>
<tr>
<td>PRA, ng/mL/h</td>
<td>-0.01</td>
<td>-0.04</td>
<td>0.01</td>
<td>0.01</td>
<td>-1.19</td>
<td>0.237</td>
</tr>
<tr>
<td>Maternal age, years</td>
<td>0.01</td>
<td>-0.01</td>
<td>0.04</td>
<td>0.01</td>
<td>1.04</td>
<td>0.298</td>
</tr>
<tr>
<td>Maternal BMI before pregnancy, kg/m²</td>
<td>0.03</td>
<td>-0.01</td>
<td>0.06</td>
<td>0.02</td>
<td>1.38</td>
<td>0.170</td>
</tr>
<tr>
<td>Oral glucose tolerance test time, day</td>
<td>0.00</td>
<td>-0.01</td>
<td>0.00</td>
<td>0.00</td>
<td>-1.67</td>
<td>0.096</td>
</tr>
<tr>
<td>Gestational age at delivery, day</td>
<td>0.00</td>
<td>-0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>-0.09</td>
<td>0.928</td>
</tr>
</tbody>
</table>

For the FBG of the PRA, aldosterone and aldosterone/PRA ratio, results of multivariable regression analysis are shown. FBG: fasting blood glucose, PRA: plasma renin activity, R²: determination coefficient, B: non-standardized regression coefficient.

For the FBG of the PRA, aldosterone and aldosterone/PRA ratio, results of multivariable regression analysis are shown. FBG: fasting blood glucose, PRA: plasma renin activity, R²: determination coefficient, B: non-standardized regression coefficient.

aldosterone into the model, the PRA are kicked out (p = 0.237), aldosterone was still significantly related to FBG (p = 0.002), (for details see Table 3D). Exclusion of hypertensive pregnancies did not influence these findings (data not shown).

The one and two hour blood glucose concentrations were not significantly related to the RAAS system markers (data not shown). The results of the multivariable models were consistent when mothers with abnormal blood glucose level and blood pressure and their children were excluded from the analysis. These results also did not change when other models (stepwise conditional enter/remove) were used.
Figure 1. Fasting blood glucose in relation to plasma renin activity (A). Fasting blood glucose in relation to plasma aldosterone (B). Scatter plot with regression line and 95% confidence interval of the mean. The correlation coefficient and probability value from bivariate regression analysis are given.
DISCUSSION

In the general population it is known that the activity of the RAAS influences insulin resistance and onset of type 2 diabetes [6-10]. However, this relationship is unknown so far in the setting of pregnancy - a physiological condition with a high risk of impairment of insulin resistance and new onset of diabetes. The current study is the first prospective study analyzing the relationship between key parameters describing the activity of RAAS and glycemic control in a cohort of 689 pregnant Chinese women. We demonstrated that FBG is inversely correlated with PRA, whereas plasma aldosterone showed a highly significant positive correlation with FBG. Moreover, plasma aldosterone was significantly higher in pregnant women with GDM as compared to those women with normal glucose tolerance. This confirms an earlier small study also showing elevated aldosterone in diabetic pregnant women [18]. Another small study showed that plasma concentrations of Ang-(1-7) were reduced in GDM patients compared to normal pregnancy [19].

The pregnancy-induced increase of plasma angiotensin (1-7) is blunted in gestational diabetes. It is of note that in our study only aldosterone remains significantly associated to fasting glucose when adding both aldosterone and PRA to the regression model. This may indicate that aldosterone is the driving force of this relationship (see Table 3D).

The prevalence of GDM in different countries is 1-14% [1,2]. The results of our study are within this range. The cohort studied here is representative for a Chinese cohort in terms of key characteristics like maternal age, maternal height, maternal body mass index before pregnancy, gestational age and birth weight [20] suggesting that our findings are of general impact.

In normal human pregnancy, there is an increase in almost all of the components of the RAAS, which is known to be involved in fetal and placental development, salt balance, and subsequent well-being of mother and fetus. The pathologic pregnancy such as preeclampsia is characterized by significant alterations in the systemic and the local uteroplacental RAAS [5]. Our study revealed that PRA was lower in preeclampsia pregnancies. This is in line with earlier reports [21]. Our study is an association study showing that FBG is inversely correlated with PRA, whereas plasma aldosterone showed a highly significant positive correlation with FBG. This study type does not allow making firm conclusions on causality. Both are possible; an alteration of the RAAS may influence glycemia during pregnancy and vice versa: altered glycemia may influence the RAAS. Even the different time points of measuring fasting glucose, on the one hand, and aldosterone and PRA, on the other hand, do not indicate causality. A clear way to figure out causality would be pharmacological interventions with ACE inhibitors or angiotensin receptor blockers (ARBs) as it was done in hypertensive study populations (see introduction). This approach, however, is not possible in pregnant women because interfering pharmacologically with the RAAS during pregnancy may induce cardiac and renal malformations of the growing fetus [22]. Thus, causality can only be proven in adequately designed animal models. On the other hand, there is good scientific evidence that the RAAS may influence primarily glycemia during pregnancy as outlined below:

The regulation of glycemic control during pregnancy is complex and far from being understood. The impact of the activity of the RAAS during pregnancy on glycemic control is unknown. However, in the past years, there has been growing evidence that the RAAS is involved in insulin resistance or new onset of type 2 diabetes [6-10]. Indeed, a glucose-responsive element has been identified on the angiotensinogen promoter [23]. A large body of data suggest that there is crosstalk between insulin signaling and RAAS at extracellular and intracellular levels [6]. Schlemm et al. demonstrated that the angiotensinogen M235T polymorphism could represent a key linking factor between the RAAS and insulin resistance as early as in utero [24]. Our data suggest that the activation of RAAS might also act on the insulin system through the above mentioned mechanisms during pregnancy. The underlying pathway in pregnancy, however, needs to be addressed in further studies.

Study limitations are the fact that the oral glucose test and RAAS system analyses were not done at the same day of gestation due to logistic/feasibility reasons. Furthermore, we just measured glucose level but not insulin. This needs to be addressed in further studies. Our study was done in an Asian population eating mainly Asian food. Since both ethnic background and also dietary salt intake may modify the activity of the RAAS, our data should be replicated in cohorts with Caucasian as well as Afro-American genetic background.

In conclusion, our study demonstrated that FBG in pregnant women is inversely correlated with the PRA, whereas plasma aldosterone showed a highly significant positive correlation with FBG during pregnancy. Moreover, plasma aldosterone is significantly higher in pregnant women with GDM compared to women with normal glucose tolerance. Given the preclinical evidence, these data may indicate that the RAAS during pregnancy contributes to glycemic control and the pathogenesis of insulin resistance/new onset of diabetes during pregnancy. However, a reverse causality - altered glycemia during pregnancy may influence key components of the RAAS - cannot be excluded.

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Declaration of Interest:
There is no conflict of interest for any of the authors.

References:

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