Diabetologia (2022) 65:541–551
https://doi.org/10.1007/s00125-021-05622-0

ARTICLE

Longitudinal changes in glucose during pregnancy in women with gestational diabetes risk factors

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Received: 7 May 2021 / Accepted: 27 September 2021 / Published online: 30 December 2021
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Abstract

Aims/hypothesis Despite recommendations to screen women with diabetes risk factors for hyperglycaemia in the first trimester, criteria for normal glucose values in early pregnancy have not been firmly established. We aimed to compare glucose levels in early pregnancy with those later in gestation and outside of pregnancy in women with diabetes risk factors.

Methods In pregnant women ($N = 123$) followed longitudinally through the postpartum period, and a separate cohort of non-pregnant women ($N = 65$), we performed 75 g oral glucose tolerance tests. All participants had one or more risk factors for diabetes. Using linear regression, we tested for differences in glucose levels between non-pregnant and pregnant women at early (7–15 weeks) and mid-late (24–32 weeks) gestation as well as postpartum, with adjustment for maternal age, parity, marital status and BMI. In a longitudinal analysis using mixed-effects models, we tested for differences in glucose levels across early and mid-late pregnancy compared with postpartum. Differences are expressed as β (95% CI).

Results Fasting glucose was lower in pregnant compared with non-pregnant women by 0.34 (0.18, 0.51) mmol/l ($p < 0.0001$) in early pregnancy and by 0.45 (0.29, 0.61) mmol/l ($p < 0.0001$) in mid-late pregnancy. In longitudinal models, fasting glucose was lower by 0.13 (0.04, 0.21) mmol/l ($p = 0.003$) in early pregnancy and by 0.16 (0.08, 0.25) mmol/l ($p = 0.0003$) in mid-late pregnancy compared with the same women postpartum. Early pregnancy post-load glucose levels did not differ from those in non-pregnant women or the same women postpartum. In mid-late pregnancy, compared with non-pregnant women, elevations in 1 h post-load glucose level (0.60 [−0.12, 1.33] mmol/l, $p = 0.10$) and 2 h post-load glucose (0.49 [−0.21, 1.19] mmol/l, $p = 0.17$) were not statistically significant. However, in longitudinal analyses, 1 h and 2 h post-load glucose levels were higher in mid-late pregnancy (by 0.78 [0.35, 1.21] mmol/l, $p = 0.0004$, and 0.67 [0.30, 1.04] mmol/l, $p = 0.0005$, respectively) when compared with postpartum.

Conclusions/interpretation In women with diabetes risk factors, fasting glucose declines in the first trimester. Post-load glucose increases later in pregnancy. These findings may inform criteria for diagnosing hyperglycaemia early in pregnancy.

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Research in context

What is already known about this subject?

- Early pregnancy hyperglycaemia screening is recommended in women with risk factors for diabetes
- It is unclear how normal glucose values in early pregnancy differ from those later in pregnancy and outside of pregnancy

What is the key question?

- How do fasting and post-load glucose levels in early pregnancy differ from levels in mid-late pregnancy, postpartum and the non-pregnant state?

What are the new findings?

- In early pregnancy, fasting glucose levels are lower than in non-pregnant women and similar to levels in mid-late pregnancy
- In early pregnancy, glucose levels after an oral glucose load are similar to levels in non-pregnant women and lower than levels in mid-late pregnancy

How might this impact on clinical practice in the foreseeable future?

- Our data support the application of gestational diabetes criteria to early pregnancy fasting glucose levels but post-load thresholds may need to be lowered in order to apply them to early pregnancy

Keywords Gestational diabetes · Glucose levels · Oral glucose tolerance testing · Pregnancy

Abbreviations

CGM	Continuous glucose monitoring
GDM	Gestational diabetes mellitus
IADPSG	International Association of the Diabetes in Pregnancy Study Groups
SPRING	Study of Pregnancy Regulation of INsulin and Glucose

Introduction

Guidelines recommend screening for hyperglycaemia in early pregnancy in women with risk factors for diabetes [1, 2]. Such screening is meant to occur in the first trimester, months earlier than conventional testing for gestational diabetes mellitus (GDM) at 24–30 weeks' gestation [1, 2]. Despite consensus that hyperglycaemia screening in early pregnancy ought to occur, there is lack of clarity regarding what glucose levels reflect euglycaemia in early pregnancy [1–5].

GDM is usually diagnosed using an OGTT in mid-late pregnancy (at 24–30 weeks' gestation). The International Association of the Diabetes in Pregnancy Study Groups (IADPSG) initially suggested that the criteria it developed for diagnosis of GDM in mid-late pregnancy could be applied to the first trimester, but with additional data this has been called into question [1–6]. American Diabetes Association (ADA) guidelines recommend screening in early pregnancy to identify cases of undiagnosed pregestational diabetes, while the American College of Obstetricians and Gynecologists endorse screening in early pregnancy to identify undiagnosed pregestational diabetes as well as cases of early GDM [1, 2].

Conflicting data about changes in blood glucose levels during pregnancy hinder the ability to generate evidence-based guidelines for the diagnosis of hyperglycaemia in early pregnancy. Glucose metabolism changes dramatically during pregnancy, with both insulin resistance and insulin secretion increasing by late gestation [7–13]. While lower fasting glucose levels have been observed in pregnant women, the gestational window during which the decline in fasting glucose occurs is not well established [5, 6, 14–17]. Most previous studies show an increase in postprandial glucose in pregnancy but it is again unclear at what point in gestation postprandial blood glucose begins to rise [11–13, 16, 18–22]. Finally, it is not certain to what extent glycaemic testing during early pregnancy reflects a person's glucose tolerance outside of pregnancy.

We examined data from a study of pregnant and non-pregnant women with risk factors for diabetes. The goal of our analysis was to determine whether fasting and OGTT glucose levels in early pregnancy differ from those in mid-late pregnancy, postpartum and the non-pregnant state. We hypothesised that glucose levels in early pregnancy would differ from those in mid-late pregnancy and outside of pregnancy.

Methods

Participants

We studied women participating in the Study of Pregnancy Regulation of INsulin and Glucose (SPRING) [23]. This was an interim analysis for a secondary purpose. Women were recruited from the obstetric practice at Massachusetts General Hospital and through advertisements in the Boston area. We enrolled pregnant participants in the first trimester for a longitudinal study and also performed a cross-sectional study of non-pregnant women. Women included in the study were required to have risk factors for GDM (e.g. overweight status indicated by BMI, plus the presence of one additional risk factor as described by the ADA, GDM in a previous pregnancy regardless of BMI, or family history of diabetes mellitus regardless of BMI) [1, 2]. We excluded women with pre-existing diabetes or who were using medications known to affect blood glucose levels (e.g. metformin, systemic glucocorticoids). The Partners Healthcare/Mass General Brigham Institutional Review Board approved the study and participants gave written informed consent.

Study design

Pregnant women were studied in early pregnancy at 7–15 weeks' gestation, in mid-late pregnancy at 24–32 weeks' gestation, and at 6–24 weeks postpartum. Non-pregnant women were studied at a single study visit. Participants filled out a questionnaire to self-report age, gravidity, parity, income, race/ethnicity and family history of diabetes. For non-pregnant participants, height and weight were measured at the study visit. For pregnant participants, height was measured at the first visit and weight was measured at each study visit. BMI was calculated based on measured height and weights. We gathered gestational age data (based on early pregnancy ultrasound or last menstrual period) from the medical record. Non-pregnant women completed an OGTT at a single study visit. Pregnant women completed OGTTs at the three study visits: in early pregnancy at 7–15 weeks' gestation; in mid-late pregnancy at 24–32 weeks' gestation; and at 6–24 weeks postpartum. In preparation for the OGTT, participants fasted for at least 8 h before a blood sample was drawn. They then consumed a 75 g standardised OGTT beverage. We drew additional blood at 30 min, 1 h and 2 h after the oral glucose load.

Blood was collected in sodium fluoride tubes for glucose testing and was sent immediately to Massachusetts General Hospital's Core Clinical Laboratory. Glucose was measured with the hexokinase method using the Cobas 8000 modular analyser (Roche Diagnostics, Basel, Switzerland; intra-assay CV <1%). We applied IADPSG criteria at both time points in pregnancy to define GDM (any of one of the following: fasting plasma glucose ≥5.1 mmol/l; 1 h post-load plasma glucose ≥10.0 mmol/l; or 2 h post-load plasma glucose ≥8.5 mmol/l) [24]. Some participants who met IADPSG criteria at their first study visit did not undergo a full OGTT later in pregnancy, as per study protocol. The fasting level for exclusion from the second OGTT changed during the study from 5.1 to 5.5 mmol/l because of the emerging consensus that criteria developed for hyperglycaemia diagnosis in mid-late pregnancy may not apply to the first trimester [4]. Women diagnosed with GDM at their first study visit who were not taking glucose-lowering medications were eligible for a fasting glucose measurement in mid-late pregnancy.

Statistical analysis

We included data from participants who had completed or dropped out of the study as of October 2020. We performed two types of analyses for each fasting or post-load glucose level. In the first, we compared glucose levels in pregnant and postpartum women to levels in non-pregnant women, which served as the reference group. For this analysis (non-pregnant reference), we tested for differences in each OGTT glucose level in early pregnancy, in mid-late pregnancy, or postpartum using three separate linear regression models after adjustment for characteristics that differed between pregnant/postpartum and non-pregnant participants (maternal age, parity, marital status and BMI). Hypothesis tests were conducted for each OGTT glucose level evaluating the null hypothesis that glucose level did not differ between pregnant/postpartum and non-pregnant women for a given study time point after adjustment for the aforementioned covariates. In our longitudinal analysis (postpartum reference), we tested for changes in glucose levels in the same women in early pregnancy, mid-late pregnancy and postpartum. For this analysis, we used linear mixed-effects models with study time point modelled as a categorical fixed effect and participant modelled as a random intercept following a normal distribution. Other fixed effects included age, personal history of GDM, Hispanic ethnicity, marital status, and completion of college (factors that were associated with participant dropout or retention), as well as BMI. Hypothesis tests were conducted for each OGTT glucose level evaluating the null hypothesis that, for a given participant, glucose level did not differ between postpartum and a given study time point after adjustment for the aforementioned covariates (i.e. fixed effects). For the linear mixed-effects model analysis, we conducted an additional sensitivity analysis limited to women who attended all three visits. We also evaluated whether a more complex correlation structure was needed for the longitudinal analysis (see electronic supplementary material [ESM] Methods).

There were two sources of missing glucose data: (1) missed visits, in which no glucose measures were collected due to participant dropout or use of glucose-lowering medications

(per protocol); and (2) incomplete visits, in which some but not all glucose measures were unmeasured due to technical issues (<3% of total glucose values) or a GDM diagnosis in the first study visit that precluded administration of the full OGTT at the mid-late pregnancy visit (n = 12 per protocol). We utilised statistical techniques to account for missing data only when it was not due to per protocol exclusions. The statistical techniques implemented were conducted under the missing at random assumption. In the first analysis (linear regression with non-pregnant reference), we combined inverse probability weighting with multiple imputation to resolve missingness due to missed and incomplete visits separately. In the longitudinal analysis (postpartum reference), multiple imputation alone was used. Multiple imputation of the outcome variable is preferred to listwise deletion (i.e. complete case analysis) in terms of both preserving statistical power and reducing bias due to missing data [25, 26]. A detailed description of the missing data approach for accounting for missingness in baseline demographic variables as well as glucose data can be found in ESM Methods.

In a secondary analysis (both for the non-pregnant reference and postpartum reference), we excluded women who met IADPSG criteria for GDM at any point in gestation. IADPSG GDM status was ascertained for participants who had either of the following: (1) fasting, 1 h post-load, and 2 h post-load glucose all below the respective IADPSG thresholds, indicating no GDM; or (2) at least one of those measurements above the respective IADPSG thresholds, indicating GDM. As such, GDM status was known for some participants who did not have all three measurements, as long as they met GDM criteria for at least one measurement.

Statistical analyses were conducted in R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Participants

Figure 1 depicts participation in the longitudinal study and ESM Table 1 provides a description of missing glucose data. Characteristics of participants at the first study visit are given in Table 1. Pregnant participants were older, more likely to be parous, and more likely to be married than non-pregnant participants. In early pregnancy, pregnant participants had higher average BMI than non-pregnant participants. Two non-pregnant women (3.1%) and nine pregnant women (7.3%) reported a history of chronic hypertension. Nineteen non-pregnant participants were taking oral contraceptives at the time of study. Table 2 lists the gestational age, BMI and glucose levels at each study time point for pregnant/postpartum participants, as well as the BMI and glucose levels for non-pregnant participants.

Fasting glucose

As compared with the non-pregnant reference group (Table 3), fasting glucose was lower in early pregnancy (β −0.34 mmol/l [95% CI −0.50, −0.18], $p < 0.0001$) and mid-late pregnancy (β −0.45 mmol/l [95% CI −0.61, −0.29], $p < 0.0001$). Fasting glucose levels in postpartum women were also lower than fasting levels in the separate

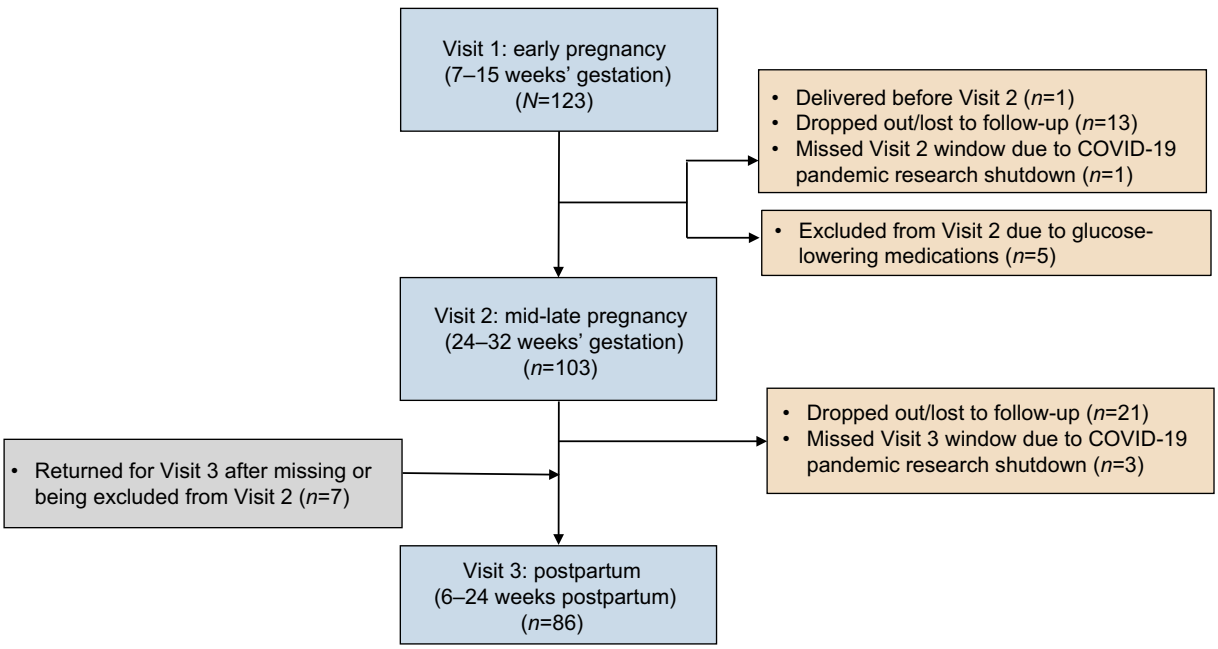

Fig. 1 Flow chart depicting the follow-up of SPRING participants for the present analysis

Table 1 Participant characteristics at first study visit

Characteristic	Pregnant/postpartum	Non-pregnant	*p* value
N	123	65	
Age, years	32.6±4.8	27.5±6.1	<0.001
BMI, kg/m^2[a]	29.8±6.8	27.5±5.4	0.02
Nulliparous	60 (48.8)	54 (83.1)	<0.001
Race/ethnicity			0.19
Hispanic/Latina	25 (20.3)	11 (16.9)	
Non-Hispanic/Latina			
White	66 (53.7)	27 (41.5)	
Black/African American	15 (12.2)	11 (16.9)	
Asian	10 (8.1)	12 (18.5)	
Other/multiple	7 (5.7)	4 (6.2)	
Family history of diabetes	45 (36.6)	31 (47.7)	0.19
Previous GDM among parous women[b]	17 (27.0)	1 (9.1)	0.37
Smoking status[c]			0.27
Never smoker	96 (80.7)	57 (87.7)	
Past smoker	22 (18.5)	8 (12.3)	
Active smoker	1 (0.8)	0 (0.0)	
Employed full-time	83 (67.5)	35 (53.8)	0.09
Married	88 (71.5)	9 (13.8)	<0.001
Completed college	105 (85.4)	52 (80.0)	0.46

Data are presented as mean ± SD or *n* (%). Percentages are calculated relative to the number of participants for whom the given characteristic is known

[a] BMI was calculated at the early pregnancy visit for pregnant participants and was missing for one pregnant participant

[b] In the pregnant/postpartum cohort, 63 participants were parous; in the non-pregnant cohort, 11 participants were parous

[c] Smoking status was missing for four pregnant participants

group of non-pregnant women (β −0.24 mmol/l [95% CI −0.41, −0.07], $p = 0.006$).

In the longitudinal analysis ($N = 123$; Fig. 2a, Table 3), fasting glucose was lower in early (β −0.13 mmol/l [95% CI −0.21, −0.04], $p = 0.003$) and mid-late pregnancy (β −0.16 mmol/l [95% CI −0.25, −0.08], $p = 0.0003$) compared with fasting glucose in the same women postpartum. These relationships were consistent with the results of the sensitivity analysis of women with complete longitudinal glucose data (ESM Table 2). There was no significant difference in fasting glucose levels between early and mid-late pregnancy (β −0.04 mmol/l [95% CI −0.12, 0.05], $p = 0.39$).

Post-load glucose

30 min As compared with the reference group of non-pregnant women (Table 3), 30 min post-load glucose levels did not differ in early pregnancy (β −0.26 mmol/l [95% CI −0.82,

Table 2 Glucose levels in pregnant and postpartum women and the non-pregnant reference group

Variable	Early pregnancy	Mid-late pregnancy	Postpartum	Non-pregnant
N	123	103	86	65
Gestational age/time postpartum, weeks	12.6±1.6	26.6±1.8	10.8±7.7	–
BMI, kg/m^2	29.8±6.8	31.7±6.0	29.9±5.9	27.5±5.4
Glucose levels, mmol/l				
Fasting	4.5±0.42	4.5±0.43	4.7±0.48	4.7±0.46
30 min post load	7.2±1.6	7.4±1.3	7.4±1.4	7.2±1.2
1 h post load	7.0±2.0	7.7±1.7	7.1±2.0	6.5±2.1
2 h post load	5.9±1.6	6.3±1.6	5.9±1.7	5.5±1.7

Data are shown as mean ± SD

Table 3 Adjusted differences between pregnancy and postpartum glucose levels in all women and after excluding women with GDM

Glucose measure	Early pregnancy				Mid-late pregnancy				Postpartum	
	Non-pregnant reference[a]		Postpartum reference[b]		Non-pregnant reference[a]		Postpartum reference[b]		Non-pregnant reference[a]	
	All women	Excluding women w/GDM	All women	Excluding women w/GDM	All women	Excluding women w/GDM	All women	Excluding women w/GDM	All women	Excluding women w/GDM
Fasting	−0.34 (<0.0001)	−0.45 (<0.0001)	−0.13 (0.003)	−0.20 (<0.0001)	−0.45 (<0.0001)	−0.50 (<0.0001)	−0.16 (0.0003)	−0.19 (<0.0001)	−0.24 (0.006)	−0.26 (0.005)
30 min post load	−0.26 (0.36)	−0.70 (0.01)	−0.12 (0.47)	−0.31 (0.09)	0.02 (0.94)	−0.11 (0.69)	0.08 (0.62)	0.02 (0.92)	−0.09 (0.75)	−0.29 (0.40)
1 h post load	0.30 (0.46)	−0.40 (0.30)	0.11 (0.61)	−0.08 (0.73)	0.60 (0.10)	0.20 (0.57)	0.78 (0.0004)	0.51 (0.03)	−0.01 (0.99)	−0.41 (0.35)
2 h post load	0.19 (0.57)	−0.36 (0.26)	0.15 (0.41)	−0.02 (0.93)	0.49 (0.17)	0.04 (0.91)	0.67 (0.0005)	0.34 (0.05)	−0.16 (0.62)	−0.44 (0.18)

Data are shown as β (*p* value)

[a] Non-pregnant reference: adjusted linear regression models include age, nulliparous status, marriage status and BMI as covariates

[b] Postpartum reference: models are longitudinal linear mixed-effects models with time point modelled as a fixed effect and participant modelled as a random effect; models are adjusted for age, personal history of GDM, Hispanic or not, marital status, completion of college or not, and BMI as covariates

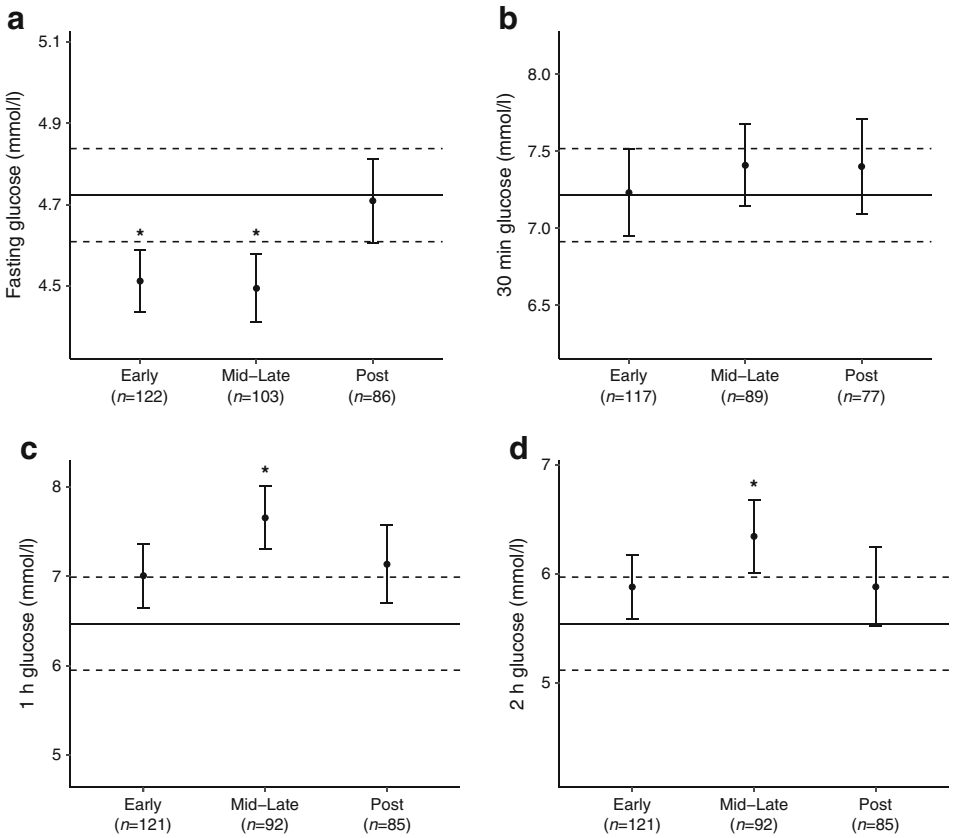

Fig. 2 Longitudinal changes in glucose levels during pregnancy and postpartum. Women were given a 75 g OGTT at three timepoints: early pregnancy (Early, 7–15 weeks' gestation), mid-late pregnancy (Mid-late, 24–32 weeks' gestation) and postpartum (Post, 6–24 weeks). Glucose levels were measured before the oral glucose load (**a**) and at 30 min (**b**), 1 h (**c**) and 2 h (**d**) after the glucose load. Error bars depict the 95% CI for each time point. The solid and dashed horizontal lines depict the point estimate and 95% CIs for glucose levels among non-pregnant participants. *$p < 0.05$ vs postpartum levels in longitudinal analyses

0.30], $p = 0.36$) or mid-late pregnancy (β 0.02 mmol/l [95% CI −0.51, 0.55], $p = 0.94$). There was also no difference between 30 min post-load glucose levels in women studied postpartum and the non-pregnant reference group (β −0.09 mmol/l [95% CI −0.67, 0.49], $p = 0.75$).

In longitudinal analyses ($N = 123$; Fig. 2b, Table 3), 30 min post-load glucose levels did not significantly differ in early (β −0.12 mmol/l [95% CI −0.44, 0.20], $p = 0.47$) or mid-late pregnancy (β 0.08 mmol/l [95% CI −0.25, 0.42], $p = 0.62$), compared with the same women postpartum. These results held true in our sensitivity analysis of women with complete glucose data (ESM Table 2).

1 h As compared with the reference group of non-pregnant women (Table 3), 1 h post-load glucose levels did not significantly differ in early pregnancy (β 0.30 mmol/l [95% CI −0.50, 1.09], $p = 0.46$). Mid-late pregnancy 1 h post-load glucose levels appeared higher in comparison with the non-pregnant reference group but this difference did not reach statistical significance (β 0.60 mmol/l [95% CI −0.12, 1.33], $p = 0.10$). There was no difference in 1 h glucose levels between postpartum women and the non-pregnant reference group (β −0.01 mmol/l [95% CI −0.79, 0.78], $p = 0.99$).

In the longitudinal analysis ($N = 123$; Fig. 2c Table 3), 1 h post-load glucose levels did not differ in early pregnancy compared with in the same women postpartum (β 0.11 mmol/l [95% CI −0.30, 0.52], $p = 0.61$). In mid-late pregnancy, 1 h post-load glucose levels were higher than postpartum levels in the same women (β 0.78 mmol/l [95% CI 0.35, 1.21], $p = 0.0004$). These relationships were consistent with those found in our sensitivity analysis of women with complete glucose data (ESM Table 2). The 1 h post-load glucose levels were also higher in mid-late pregnancy in comparison with early pregnancy (β 0.68 mmol/l [95% CI 0.27, 1.08], $p = 0.001$) in the same women.

2 h As compared with the non-pregnant reference group (Table 3), 2 h post-load glucose levels did not differ in early pregnancy (β 0.19 mmol/l [95% CI −0.48, 0.86], $p = 0.57$) or mid-late pregnancy (β 0.49 mmol/l [95% CI −0.21, 1.19], $p = 0.17$). There was also no difference between 2 h post-load glucose levels in women studied postpartum and the non-pregnant reference group (β −0.16 mmol/l [95% CI −0.82, 0.49], $p = 0.62$).

In longitudinal analyses ($N = 123$; Fig. 2d, Table 3), 2 h post-load glucose levels did not differ in early pregnancy (β 0.15 mmol/l [95% CI −0.20, 0.50], $p = 0.41$) compared with the same women postpartum. In mid-late pregnancy, 2 h post-load glucose levels were higher than in the same women postpartum (β 0.67 mmol/l [95% CI 0.30, 1.04], $p = 0.0005$). These results were consistent with those found in our sensitivity analysis of women with complete longitudinal glucose

data (ESM Table 2). The 2 h post-load glucose levels were higher in mid-late pregnancy in comparison with early pregnancy (β 0.52 mmol/l [95% CI 0.17, 0.87], $p = 0.004$) in the same women.

Women without GDM

In early pregnancy, 120 participants had known GDM status, 17 of whom (14.2%) met criteria for GDM. In mid-late pregnancy, 12 of 88 (13.6%) participants with adequate data for GDM ascertainment who did not have GDM in early pregnancy met GDM criteria. Results of analyses after excluding women meeting GDM criteria at either timepoint are shown in Table 3.

In the comparison with the non-pregnant reference group, exclusion of women with GDM increased the magnitude of the reduction in fasting glucose in early pregnancy and mid-late pregnancy (Table 3). The differences in fasting glucose between postpartum and the separate group of non-pregnant women were similar to the analysis that included women with GDM. In longitudinal models, the difference in fasting glucose in early pregnancy as compared with postpartum increased in magnitude when women with GDM were excluded (Table 3).

Unlike in the primary analysis, 30 min post-load glucose levels were significantly lower in early pregnancy compared with the non-pregnant reference group when excluding women who met GDM criteria (β −0.70 mmol/l [95% CI −1.24, 0.15], $p = 0.01$; Table 3). Like in the primary analysis, 1 h and 2 h post-load glucose in early pregnancy in women without GDM were similar to those in the non-pregnant reference group. The relationships observed in the longitudinal analysis of early pregnancy post-load glucose levels compared with postpartum levels after excluding women with GDM were consistent with the results of the primary analysis; although 30 min post-load glucose in early pregnancy was lower, compared with postpartum, after exclusion of women with GDM, the difference did not reach statistical significance (β −0.31 mmol/l [95% CI −0.67, 0.049], $p = 0.09$).

The 1 h post-load glucose in mid-late pregnancy, as compared with the non-pregnant reference group, was no longer elevated after exclusion of women with GDM. Consistent with the primary analysis, the post-load glucose levels in postpartum women were similar to those in the non-pregnant reference group when excluding women with GDM. In the longitudinal analysis, excluding women with GDM attenuated (but did not eliminate) elevations in glucose at 1 h and 2 h post load observed in mid-late pregnancy as compared with postpartum observed in the primary analysis (Table 3).

Discussion

In this study of pregnant women with diabetes risk factors, we demonstrate that fasting glucose is 0.1–0.2 mmol/l lower on average in the first trimester as compared with fasting glucose outside of pregnancy; these lower fasting glucose levels are maintained through 24–32 weeks' gestation. Early pregnancy 1 h and 2 h post-load glucose levels are similar to those outside of pregnancy but rise by 0.7 mmol/l by 24–32 weeks' gestation on average. Our data suggest that the criteria for abnormal fasting glucose currently in use for GDM diagnosis later in pregnancy could be applied in the first trimester. In contrast, the post-load glucose thresholds for GDM may need to be lowered to identify the same group of women that would be identified in mid-late gestation.

Our results suggest that fasting glucose levels decrease prior to the time of first trimester screening for hyperglycaemia and remain constant through 24–32 weeks' gestation. A 1973 study in 19 women across pregnancy beginning at 10 weeks' gestation found that fasting glucose levels in pregnancy were reduced compared with fasting glucose levels measured postpartum [14]. Since then, multiple studies have demonstrated reduced fasting glucose levels in pregnant women [5, 6, 12, 15–17, 27]. However, there are conflicting data regarding when the reduction in fasting glucose takes place. Our findings are consistent with the results of a 1998 study of 316 women that demonstrated a reduction in fasting glucose between gestational weeks 6 and 10 with no further change during pregnancy [15]. Additionally, congruent with our findings, though without data from the first trimester, a 2008 study that used continuous glucose monitoring (CGM) and OGTTs to assess blood glucose levels across pregnancy concluded that fasting glucose remained unchanged after 16 weeks' gestation [16]. Large cross-sectional studies from China and Israel, in contrast, have shown reduction of fasting glucose levels between the end of the first trimester and later in pregnancy [6, 17]. The cross-sectional nature of these analyses, as well as their larger sample sizes (providing increased power to detect small differences of uncertain clinical significance) may explain the discrepancy between these results and our own. We were unable to determine definitively from our analysis whether fasting glucose levels in the postpartum state are lower than those in other non-pregnant women. Given the widespread use of fasting OGTTs to diagnose glucose intolerance in the postpartum setting, this deserves further study.

In contrast to the reduction in fasting glucose levels, the rise in post-load glucose levels does not appear to be an early pregnancy phenomenon. We are unaware of other studies that have compared post-load glucose in early pregnancy vs outside of pregnancy. Our findings demonstrate that the elevation in post-load glucose takes place after 15 weeks' gestation and align with other studies that have shown that postprandial glucose is elevated in late pregnancy [11–13, 16, 18–22, 28]. For example, a study by Cousins et al in 1980 concluded that postprandial glucose was elevated at 35–37 weeks' gestation but not at 22–26 weeks' gestation [18]. Our study provides evidence for the presence of this elevation in gestational

weeks 24–32, a conclusion supported by Siegmund et al.'s CGM study, which found a continuous rise in postprandial glucose from the 16th to the 36th week of pregnancy, as well as a Spanish study that demonstrated an increase in post-load glucose levels between early and late pregnancy [16, 28].

Evidence suggests that that the association between glucose levels and adverse pregnancy outcomes occurs on a continuum without a clear cut point [29]; thus the exact thresholds used for the IADPSG definition of GDM in mid-late pregnancy are somewhat arbitrary. However, the possibility of reduced post-load glucose levels in early pregnancy after exclusion of women with GDM implies that some women with robust beta cell function and preserved insulin sensitivity experience a pregnancy-induced enhancement of glucose tolerance in the first trimester [30]. The existence of a subset of women for whom glucose tolerance improves implies that early pregnancy glucose results cannot be presumed to reflect blood glucose levels outside of pregnancy. Thus, guidelines that suggest that the diagnosis of diabetes which preceded pregnancy can be made in the first trimester may need to be revisited. Interestingly, women without GDM also may not experience the same degree of late pregnancy glucose intolerance that has been well described in previous studies [11, 16, 20, 21, 31].

The glycaemic changes we observed can be understood in the context of the changes in insulin physiology that occur during pregnancy. Lower fasting glucose levels in early pregnancy may be explained by an increase in insulin secretory response and sensitivity during this time, possibly in conjunction with the dilutional effects of increased plasma volume [7, 30–32]. Further, our data suggest that 30 min post-load glucose levels are reduced in early pregnancy in women without GDM; this may be a result of the robust first trimester increase in insulin secretory response characterised in our prior study [30]. A decrease in peripheral insulin sensitivity between early and late pregnancy is likely responsible for the increase in postprandial glucose during mid-late pregnancy that we observed [9–11, 30].

The results of our study may help to inform appropriate diagnostic criteria for early pregnancy hyperglycaemia in women with GDM risk factors. Specifically, if the goal in early pregnancy is to identify women who will be diagnosed with GDM later in gestation, thresholds for post-load glucose levels in early pregnancy might need to be around 0.7 mmol/l lower than conventional GDM thresholds. Our data do support the application of fasting glucose criteria developed for diagnosing GDM in mid-late pregnancy to first trimester fasting glucose levels. Studies examining the relationship between early pregnancy glucose levels and perinatal outcomes may further inform guidelines for early pregnancy diagnostic thresholds. Future studies should also examine the relationship between early pregnancy glucose level and the diagnosis of type 2 diabetes postpartum. A recent trial of early GDM screening and treatment in women with obesity applying GDM criteria developed for mid-late pregnancy to women at 14–20 weeks' gestation failed to demonstrate an improvement in perinatal outcomes with early screening [33]; future interventional studies should test alternative diagnostic thresholds for early pregnancy.

A major strength of our study is the inclusion of comparisons between glucose values in pregnancy and those in both a non-pregnant reference group and the same women postpartum. The inclusion of a longitudinal comparison allowed us to address the limitation that several characteristics of the non-pregnant reference group differed from those in the pregnant/postpartum cohort. By including women with risk factors for GDM, our study is relevant to the population that is subject to first-trimester screening [1, 2]; yet, this is also a potential limitation, as restriction to this at-risk population may limit generalisability. Our study is limited by the size of our cohort and by a lack of availability of longitudinal measurements in all participants; to address this, we combined inverse probability weighting and multiple imputation to account for missing data.

In conclusion, our study illustrates the dynamic alterations in fasting and post-load blood glucose levels that begin in early gestation and change across pregnancy in women with risk factors for diabetes. Our findings support the application of fasting glucose criteria developed for diagnosing GDM to the first trimester and suggest that post-load glucose criteria for diagnosing GDM may need to be lowered for application in early pregnancy. Ultimately, interventional trials will be required to determine to what extent glucose-lowering treatment based on novel early pregnancy glycaemic criteria improves pregnancy outcomes.

Supplementary Information The online version contains peer-reviewed but unedited supplementary material available at https://doi.org/10.1007/s00125-021-05622-0.

Acknowledgements Portions of this study in abstract form were presented at the 79th ADA Scientific Sessions, June 2019 in San Francisco.

Data availability Restrictions apply to the availability of the data that support the findings of this study. Data are available from the authors upon reasonable request and with permission of Mass General Brigham Committee on Human Research.

Funding CEP is supported by NIH K23DK113218 and the Robert Wood Johnson Foundation's Harold Amos Medical Faculty Development Program. The SPRING cohort is supported by these awards plus NIH R01HD094150. Grant nos UL1TR001102 and 8 UL1 TR000170, Harvard Clinical and Translational Science Center, from the National Center for Advancing Translational Science, also provided support for data collection in SPRING. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Research Resources, the National Center for Advancing Translational Science or the National Institutes of Health. JST is supported by NIH K23DK120874. MFH is supported by ADA's

Pathways Award no. 1-15-ACE-26. EAR is supported by NIH T32DK007529.

Authors' relationships and activities The authors declare that there are no relationships or activities that might bias, or be perceived to bias, their work.

Contribution statement CEP and RT conceptualised and designed the cohort study. JA, MJC, MC, JST and CEP acquired the data. TT, CEP, MBD and KJ designed the analyses presented in this manuscript. TT, CY and KJ performed the analyses. MBD, JA, TT, KJ, EAR, JST, SNB, MFH, RT and CEP interpreted the data. MBD, JA and CEP drafted the manuscript. All authors revised the manuscript critically for intellectual content and approved the final version to be published. CEP is responsible for the integrity of the work as a whole.

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