

# Glucose Absorption in Gestational Diabetes Mellitus During an Oral Glucose Tolerance Test

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**OBJECTIVE**—Women with gestational diabetes mellitus (GDM) show reduced insulin sensitivity and markedly elevated glucose excursions. After delivery, GDM mostly reverts to normal glucose tolerance (NGT), although leaving an increased risk of type 2 diabetes. Because gastrointestinal function changes during pregnancy causing vomiting, constipation, or reduced motility, we thought that gut glucose absorption in GDM or pregnancy might be altered to affect circulating glucose excursions.

**RESEARCH DESIGN AND METHODS**—By undergoing 180-min oral glucose tolerance tests (OGTTs), pregnant women with GDM (GDM<sub>preg</sub>;  $n = 15$ , BMI =  $32 \pm 2$  kg/m<sup>2</sup>, aged  $33 \pm 1$  years) were compared with NGT women (NGT<sub>preg</sub>;  $n = 7$ , BMI =  $28 \pm 1$  kg/m<sup>2</sup>, aged  $34 \pm 2$  years), matching for major anthropometric characteristics (each  $P > 0.2$ ). After delivery (6–7 months later), both groups were studied the same way. We computed and mathematically modeled gut glucose absorption from insulin-mediated glucose disappearance and endogenous glucose production (EGP). Whole-body insulin sensitivity was calculated using the Clamp-like Index.

**RESULTS**—GDM<sub>preg</sub> showed 16–25% higher plasma glucose concentrations ( $P < 0.04$ ) during the final 2 h of OGTT, similar EGP, but lower ( $P < 0.01$ ) insulin sensitivity ( $2.7 \pm 0.2$  mg · kg<sup>-1</sup> · min<sup>-1</sup> vs. NGT<sub>preg</sub>:  $4.5 \pm 0.8$  mg · kg<sup>-1</sup> · min<sup>-1</sup>). In GDM<sub>preg</sub>, gut glucose absorption rates were  $\leq 52\%$  lower from 30 to 120 min ( $P < 0.03$  vs. conditions after delivery or NGT<sub>preg</sub>). In contrast, glucose absorption rates in NGT<sub>preg</sub> were comparable during and after pregnancy. None of the studied women developed diabetes after delivery.

**CONCLUSIONS**—In GDM<sub>preg</sub>, OGTT gut glucose absorption is markedly lower during hyperglycemia, whereas both glycemia and glucose absorption in NGT<sub>preg</sub> are comparable between pregnant and postpartum states. Thus, hyperglycemia in GDM does not seem to result from too rapid or increased glucose absorption.

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**W**omen with gestational diabetes mellitus (GDM) display both impaired  $\beta$ -cell function and reduced sensitivity to insulin, bearing an elevated risk to develop type 2 diabetes in the future (1–3). Because GDM may result in newborn macrosomia and other disorders (4), the World Health Organization and the International Association of

Diabetes and Pregnancy Study Groups recommend the standardized, 75-g oral glucose tolerance test (OGTT) at 24 weeks' gestation or later to diagnose GDM (2). By focusing on sex-related differences, we have most recently investigated gut glucose absorption by using 180-min OGTTs in a healthy cohort of both sexes (5). We found that women, when compared with

men, show differences in gut glucose absorption; intestinal uptake of glucose in women is lower in the early phase but higher in the late OGTT phase and may also contribute to elevated OGTT glucose concentrations in women at 120 min, which several epidemiologic studies have shown, as summarized in detail previously (5).

There is evidence that during pregnancy the function of the gastrointestinal tract is altered; on the one hand, symptoms such as nausea, vomiting, and constipation (6) occur, and on the other hand, gastrointestinal transport and motility are diminished (6), most likely because of reduced endogenous prokinetic peptide release (7). Thus, we hypothesized that in pregnant women, when compared with nonpregnant conditions, glucose absorption might be further decreased because of propulsion delay and could thereby also affect glucose excursions. Conversely, pronounced glucose excursions in GDM might be the result of too rapid gastrointestinal transport/glucose absorption.

Thus, we aimed to compare glucose absorption during 180-min OGTTs in women during pregnancy and subsequently after delivery with 1) normal glucose tolerance (NGT) with women with 2) GDM, without differences in major anthropometric characteristics. We applied our recently developed method that allows estimation of glucose absorption during OGTT without infusion of (radio-)labeled isotopes (5).

## RESEARCH DESIGN AND METHODS

### Study participants

Of those women participating in a prospective longitudinal follow-up [Vienna postgestational diabetes project (8)], most women were examined in a 120-min OGTT (which is essential for GDM diagnosis), but a total of 22 women agreed to undergo a 180-min OGTT at the end of the second trimester and after delivery. We only included those women who had undergone a 180-min OGTT, because examination during a 120-min OGTT

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seemed not to be sufficient to study the entire glucose absorption process. The pregnant study participants were divided into two groups, depending on whether they had NGT (“NGT<sub>preg</sub>”) or GDM (“GDM<sub>preg</sub>”) (2). All subjects were studied again postpartum using the same protocol (i.e., “NGT after delivery” and “former GDM after delivery”) (Table 1). GDM and diabetes (for the nonpregnant subjects) were defined as reported (2,9). All women gave informed and written consent before participating in the study.

**75-g OGTT**

Glucose tolerance was tested by an OGTT (2,9,10) after ingestion of a 75-g glucose solution (Glucos-Drink75, Roche Diagnostics, Vienna, Austria). Blood samples for routine laboratory analysis were drawn at baseline for determination of plasma glucose, serum insulin, and serum C-peptide at 0, 10, 20, 30, 60, 90, 120, 150, and 180 min and measured as described (5,8,11). Plasma concentrations of free fatty acids (FFAs) were measured at fasting using a microfluorimetric assay from Wako (Richmond, VA) (5).

**Gut glucose absorption**

Intestinal glucose absorption during OGTT was calculated as recently described and

validated (5). The Clamp-like Index (CLIX), whose values closely approach M-values from the clamp test (10,12), was used for insulin sensitivity measurement (13). In brief, the increase of postprandial circulating glucose (dgluc<sub>circ</sub>) over time (dt) is the result of gain from gut glucose absorption (ABS) and EGP, and loss because of glucose uptake (R<sub>d</sub>), predominantly by skeletal muscle. Thus, changes in glucose concentration over time can be expressed as

$$dgluc_{circ}/dt = 1/V_G \times [BW \times (EGP - R_d) + ABS] \quad (1)$$

with initial condition: gluc(0) = fasting glucose concentration; ABS(0) = 0; and EGP(0) = R<sub>d</sub>(0). BW is the body weight, and V<sub>G</sub> is the oral glucose distribution volume assumed as ~15% of BW (5). To ensure that the glucose distribution volume is not different during pregnancy, we carried out intravenous glucose tolerance tests in pregnant GDM (n = 7, BMI = 32 ± 3 kg/m<sup>2</sup>), nonpregnant lean (n = 5, BMI = 23 ± 1 kg/m<sup>2</sup>), and obese (n = 7, BMI = 35 ± 2 kg/m<sup>2</sup>) women and found no differences in the calculated V<sub>G</sub> among those groups (data not shown).

We have most recently demonstrated that EGP and R<sub>d</sub> are predominantly regulated by circulating insulin concentrations

(5). EGP in women can be calculated using the following relationship (5):

$$EGP = 1.889 - 0.342 \times \ln[\text{insulin}] \quad (2)$$

R<sub>d</sub> was assessed by the logarithmic relationship, on the one hand, between fasting insulin concentrations and fasting EGP that equals fasting R<sub>d</sub>, and on the other hand, between the CLIX and the highest insulin concentration during the OGTT, as described and used for the validation group in the study by Anderwald et al. (5).

For each participant, total glucose absorbed was calculated by integrating glucose absorption rates over the 180-min OGTT. Glucose half-life in the gastrointestinal tract was individually determined by linear curve interpolation of relative glucose retention during the OGTT by using the closest time points to cross the 50% threshold (5). Equation (1) was implemented using Matlab (MathWorks Inc., Boston, MA), and gut glucose absorption was modeled by solving nonlinear least-squares problem fitting the plasma glucose values during the OGTT. Common criteria of model performance (best fit, residuals, variance-covariance Fisher matrix) were evaluated for accepting the final model prediction.

β-Cell function was assessed by the Insulinogenic Index (IGI) for the first 30 min of the OGTT, as described in detail (14).

**Table 1—Anthropometric and baseline laboratory measurements and 2-h post-OGTT plasma glucose levels of the four groups consisting of women with NGT and GDM during pregnancy and after delivery**

	NGT during pregnancy	GDM during pregnancy	NGT after delivery	Former GDM after delivery
N	7	15	7	15
Body height (cm)	168 ± 2	162 ± 2	168 ± 2	162 ± 2
Body weight (cm)	81.0 ± 6.1	83.9 ± 4.4	76.5 ± 6.4#	79.7 ± 4.7#
BMI (kg/m <sup>2</sup> )	28.4 ± 1.4	32.0 ± 1.7	26.8 ± 1.5#	30.3 ± 1.7#
Age (years)	34 ± 2	33 ± 1	34 ± 2#	34 ± 1#
Serum creatinine (mg/dL)	0.64 ± 0.03	0.58 ± 0.03	0.80 ± 0.07#	0.75 ± 0.04 #
Serum triglycerides (mg/dL)	252 (101)	161 (65)	79 (111)#	85 (92)#
Serum cholesterol (mg/dL)	261 ± 17	235 ± 14	193 ± 9#	218 ± 18
Serum HDL cholesterol (mg/dL)	83 ± 11	69 ± 4	61 ± 4	60 ± 5#
HbA <sub>1c</sub> (%)	5.1 ± 0.1	5.2 ± 0.1	5.5 ± 0.2#	5.5 ± 0.1#
FFAs (μmol/L)	424 ± 52	566 ± 36*	434 ± 72	612 ± 44*
Gestational week	27.1 ± 0.7	25.5 ± 0.4*	—	—
OGTT				
Fasting glucose (mg/dL)	83 ± 2	91 ± 3	93 ± 3#	94 ± 3
1-h Post-OGTT plasma glucose (mg/dL)	159 ± 7	194 ± 4*	161 ± 19	171 ± 8#
2-h Post-OGTT plasma glucose (mg/dL)	127 ± 6	152 ± 6*	126 ± 14	122 ± 9#

Data are given as means ± SE except for triglycerides: median (interquartile range); paired Student *t* test for intraindividual analyses, unpaired Student *t* test for NGT vs. GDM during pregnancy and after delivery. \**P* < 0.04 GDM vs. NGT. #*P* < 0.02 after vs. during pregnancy.

**Statistical analyses**

Before further analysis, normal distribution of the variables was tested by applying the Kolmogorov-Smirnov test for the entire study population and each subgroup separately (11). This test showed that all of the continuous variables except for serum triglycerides were normally distributed. Therefore, serum triglycerides were logarithmically transformed to achieve normal distributions, and statistical tests were then applied. All normally distributed data are given as means ± SEM; serum triglyceride concentrations are given as median with interquartile range. Intraindividual comparisons within each group were analyzed with the paired, two-tailed Student *t* test. Comparisons between both groups were done with the unpaired, two-tailed Student *t* test. The nonparametric Kendall rank correlation coefficient was used for correlation analysis. Differences were considered statistically significant at *P* values ≤ 0.05.

## RESULTS

### Anthropometry and basal routine laboratory measurements

Of the 22 pregnant women undergoing a 180-min OGTT, 7 and 15 subjects had NGT and GDM, respectively. GDM<sub>preg</sub> and NGT<sub>preg</sub> had comparable BMI and age as major anthropometric characteristics, as well as serum concentrations of creatinine, total and HDL cholesterol, and glycated hemoglobin A1C (HbA<sub>1c</sub>). Serum triglycerides were not different between the groups and decreased after giving delivery in GDM and NGT (each  $P < 0.01$ ). During and after pregnancy, GDM had higher fasting (each  $P < 0.04$ ) plasma FFA than NGT. With regard to gestational age, GDM<sub>preg</sub> were studied approximately 12 days earlier ( $P < 0.04$ ) than NGT<sub>preg</sub> (Table 1).

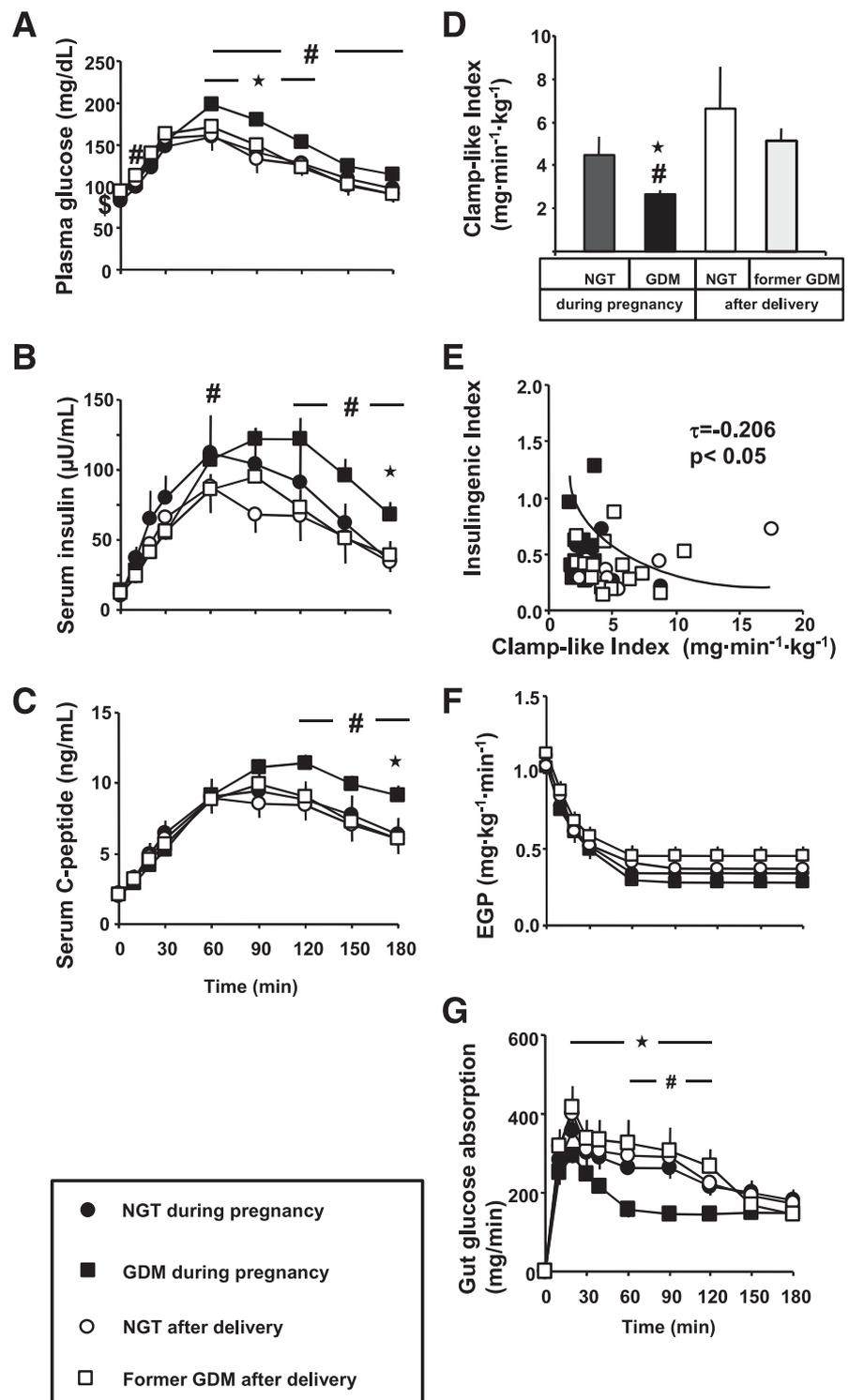
After delivery, both groups were similar in BMI, age, and levels of creatinine, lipids, and HbA<sub>1c</sub>. However, when comparing both NGT and GDM after delivery with conditions during pregnancy, BMI and serum lipids decreased, whereas serum creatinine and HbA<sub>1c</sub> increased (each  $P < 0.02$ ).

### 75-g OGTT

In NGT, fasting plasma glucose after delivery was 12% higher ( $P < 0.02$ ) (Fig. 1A, Table 1). Plasma glucose was lower at 10 min in GDM<sub>preg</sub> ( $P < 0.01$  vs. after delivery), but thereafter increased in GDM<sub>preg</sub> in the 2nd h, when compared with NGT<sub>preg</sub> (each  $P < 0.03$ ), and during the final 2 h, when compared with conditions after delivery (each  $P < 0.04$ ) (Fig. 1A). Serum insulin concentrations were elevated in GDM<sub>preg</sub> at 180 min, when compared with NGT<sub>preg</sub> ( $P < 0.03$ ), and at 60 min and from 120 to 180 min in comparison with postpartum conditions (each  $P < 0.04$ ) (Fig. 1B). Serum C-peptide was higher in the 3rd OGTT h in GDM<sub>preg</sub> ( $P < 0.04$  vs. after delivery or NGT<sub>preg</sub>), whereas the other groups displayed a similar time course of C-peptide (Fig. 1C). After delivery, none of the former GDM or NGT women developed diabetes, as confirmed by the OGTT.

### Whole-body insulin sensitivity

The GDM<sub>preg</sub> had a 40% lower ( $P < 0.01$ ) CLIX than the NGT<sub>preg</sub>. However, after delivery, insulin sensitivity improved in the women with former GDM ( $P < 0.001$ ) and was similar to that in women with NGT after delivery. Insulin sensitivity in women with NGT was comparable



**Figure 1**—Circulating concentrations of (A) glucose, (B) insulin, and (C) C-peptide, as well as (D) the CLIX, (E) correlation ( $\tau = -0.206$ ,  $P < 0.05$ ) of the CLIX with the IGI, (F) EGP, and (G) gut glucose absorption in pregnant women with NGT during pregnancy (●,  $n = 7$ ) or GDM (■,  $n = 15$ ), all of whom were studied again under identical conditions after delivery: NGT (○) and former GDM (□). Unpaired Student *t* test: \* $P < 0.03$  GDM vs. NGT during pregnancy; paired Student *t* test: # $P < 0.05$  GDM during pregnancy vs. after delivery, \$ $P < 0.02$  NGT during pregnancy vs. after delivery.

during pregnancy and after delivery (Fig. 1D).

### **β-Cell function**

IGI in NGT<sub>preg</sub> ( $0.419 \pm 0.070$ ) was similar to that in GDM<sub>preg</sub> ( $0.536 \pm 0.070$ ), in whom IGI decreased ( $P < 0.04$ ) after delivery ( $0.391 \pm 0.053$ ) and was then comparable to NGT after giving birth ( $0.389 \pm 0.065$ ). Figure 1E displays the inverse relationship between β-cell function and insulin sensitivity ( $\tau = -0.206$ ,  $P < 0.05$ ).

### **Endogenous glucose production**

All four groups showed similar endogenous glucose production (EGP) both at fasting and during OGTT (Fig. 1F).

### **Gut glucose absorption**

The GDM<sub>preg</sub> showed markedly lower gut glucose absorption rates than NGT<sub>preg</sub> (60–120 min, each  $P < 0.03$ ) and when compared with conditions after delivery (20–120 min, each  $P < 0.03$ ) (Fig. 1G). Gut absorption in women with NGT during pregnancy did not change after delivery. Total glucose absorbed during 180-min OGTT was lower in GDM<sub>preg</sub> ( $31 \pm 2$  g), when compared with conditions after delivery ( $47 \pm 6$  g,  $P < 0.01$ ) or NGT<sub>preg</sub> ( $43 \pm 5$  g,  $P < 0.02$ ), whose total glucose amount absorbed did not change after giving birth ( $46 \pm 5$  g). Glucose half-life in the gastrointestinal tract was similar in all four groups (GDM<sub>preg</sub>:  $76 \pm 3$  min, NGT<sub>preg</sub>:  $76 \pm 5$  min, former GDM after delivery:  $73 \pm 4$  min, NGT after delivery:  $71 \pm 5$  min; each  $P > 0.25$ ) and negatively correlated with body height ( $\tau = -0.288$ ,  $P < 0.01$ ), but not BMI.

To compensate for differences in body mass (nonsignificant) and gestational age, we performed a precise pair-match (seven control subjects with seven GDM subjects). The analysis yielded that the results remained almost the same regarding the study's main focus (i.e., gut glucose absorption; data not shown).

**CONCLUSIONS**—The current study investigated whether 1) gut glucose absorption is altered during pregnancy and 2) GDM is the result of elevated or accelerated gastrointestinal absorption. To this end, we performed OGTTs in 22 pregnant women (15 with GDM and 7 with NGT) and repeated the procedure ~3 months after delivery. We also assessed whole-body insulin sensitivity and β-cell function. Our novel, noninvasive modeling approach allowed us to calculate both

EGP and gut glucose absorption in pregnant women, which to the best of our knowledge has never been done before.

This study's main findings are 1) GDM<sub>preg</sub> show pronounced insulin resistance, compared with NGT<sub>preg</sub> and conditions after delivery, when they show a nondiabetic glucose metabolism; 2) β-cell function is increased in GDM<sub>preg</sub> and inversely relates to whole-body insulin sensitivity in all subjects; 3) fasting and post glucose-load EGP are comparable in all groups; and 4) gut glucose absorption is reduced in GDM<sub>preg</sub> but normalizes after delivery.

### **Whole-body insulin sensitivity and β-cell function**

It has been known for a while that pregnancy has the potential to induce pronounced insulin resistance (15). In our study participants, the GDM<sub>preg</sub> were more insulin resistant than the NGT<sub>preg</sub>, which is in line with previous reports (15). Low insulin sensitivity is also associated with increased lipid availability (11), especially elevated circulating FFAs, which were actually higher in the GDM<sub>preg</sub>.

In the presence of insulin resistance, the β-cells attempt to compensate by increasing insulin release, aiming to maintain a normal glucose metabolism, also during a glucose challenge. Despite increased insulin secretion, the GDM<sub>preg</sub> were not able to keep OGTT glucose concentrations within the nondiabetic range. Thus, the increase in β-cell function was at least in part insufficient to compensate for that pronounced degree of insulin resistance in the GDM<sub>preg</sub>. Our findings of an inverse relationship between β-cell function and whole-body insulin sensitivity have already been discussed by Buchanan (15) and are therefore completely in agreement.

### **Endogenous glucose production**

Our mathematic modeling allows for calculation of EGP during an OGTT, as validated by the gold standard, the double-tracer technique (5). In this study, we found that EGP does not change during pregnancy, regardless of the presence of GDM or NGT. However, it should be added that in diabetes, the increase in fasting glucose is the result of elevated EGP (16). Fasting glucose in our GDM<sub>preg</sub> was on average comparable to that postpartum and that in NGT<sub>preg</sub>. Thus, it does not seem surprising that fasting EGP was not elevated in GDM<sub>preg</sub>. However,

it cannot be ruled out that in a GDM cohort with markedly elevated fasting glucose concentrations, EGP would be increased as well.

In addition, Catalano et al. (17) investigated EGP in women during and after pregnancy and found that, regardless of NGT or GDM presence, basal EGP in early pregnancy (12–14 weeks) was similar to that in nonpregnant conditions. However, in late pregnancy (34–36 weeks), basal EGP was higher. Suppression of EGP by insulin was also similar in nonpregnant conditions and early pregnancy, again regardless of NGT or GDM presence. The women in our study were in the 26–27th week of pregnancy, thus just in the middle between early and late pregnancy. By combining our current and previous (17) observations, it seems that (basal) EGP during pregnancy does not increase until the very late period.

### **Gut glucose absorption**

In GDM<sub>preg</sub>, gut glucose absorption was markedly reduced by up to ~50% from 30 to 120 min, when compared with postpartum conditions or the NGT<sub>preg</sub> group (60–120 min; Fig. 1G). In NGT during and after pregnancy, and the GDM postpartum group, approximately two-thirds of the entire glucose load could be found in the circulation. This is not surprising because a substantial part of the entire load is thought to escape absorption (5,18). In contrast, in the GDM<sub>preg</sub> less than one-half of the total glucose ingested appeared in the bloodstream within the first 3 h. Gut glucose half-life was similar in all groups, suggesting that the absorption process in GDM<sub>preg</sub> was somewhat reduced as a whole.

### **Possible mechanisms**

Orocecal transit time increases in the course of pregnancy (6), but gastric emptying remains unaffected in the second or third trimester of pregnancy (19,20). In addition, the gastrointestinal smooth-muscle stimulating hormone motilin is lower in pregnant women (7). On the other hand, hyperglycemia and hyperinsulinemia also reduce gastrointestinal motility and transit time in healthy humans (21,22). Thus, gut glucose absorption in type 2 diabetic and critically ill patients with hyperglycemia is diminished (23,24). Taken together, the lower glucose absorption rates found in GDM<sub>preg</sub> seem understandable and might be due to 1) hyperglycemia, 2) hyperinsulinemia,

and/or 3) reduced prokinetic hormones during pregnancy. It should be considered that women with NGT had similar gut absorption rates during and after pregnancy (Fig. 1G); thus, the effect by reduced prokinetic motilin seems minor. However, it cannot be ruled out that the combination of hyperglycemia, hyperinsulinemia, and reduced motilin per se exerted a much greater effect in GDM than each of them solely.

### Clinical relevance

Our study demonstrates that gut glucose absorption is lower in GDM<sub>preg</sub>, in particular during their greatest glucose excursions (60–120 min); thus, hyperglycemia in GDM seems not to be due to increased or too rapid glucose absorption, but rather to pronounced insulin resistance and the failure of  $\beta$ -cells to fully compensate.

### Limitations

Glucose absorption rates at 180 min were small, but still existent, with  $\sim 0.15$ – $0.18$  g/min. Thus, in the 4th h after glucose ingestion, a small proportion ( $\leq 10$  g) of the glucose load is expected to be absorbed as well, which could have been seen during a prolonged designed examination period.

The studied sample size was rather small, which is in part due to strict legislature and other ethics guidelines for studies in pregnant women. Of note, several other interesting investigations (6,17,19) have therefore included only between one and two dozen women. In addition, gestational age was statistically different between the two pregnant groups. This can be explained in that all pregnant women were asked to participate between the 24th and 28th gestational week. Most likely by chance, the GDM were studied a few days earlier, which, however, turned out to be statistically significant (Table 1). When looking at a precise pair-match, in which the gestational age was similar, the main readouts remained nearly identical to those presented; thus, we conclude that the impact of different gestational age might be negligible.

### Major conclusion

In GDM<sub>preg</sub>, gut glucose absorption during an OGTT is markedly lower despite marked hyperglycemia, whereas NGT women show no differences in both glycemia and gastrointestinal glucose absorption when comparing conditions during pregnancy with those after delivery.

Thus, hyperglycemia in GDM does not seem to result from a too rapid or increased gastrointestinal glucose absorption.

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C.A. carried out additional experiments, analyzed data, and wrote and revised the manuscript. A.T. performed data analysis, contributed to discussion, and reviewed and edited the manuscript. Y.W. researched data. M.K. reviewed and edited the manuscript. C.W. researched data. M.G.B. and A.L. reviewed and edited the manuscript. G.P. performed mathematic calculations, participated in carrying out the additional experiments, and edited the manuscript for revision. A.K.-W. researched data, performed data analysis, contributed to discussion, and reviewed and edited the manuscript.

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