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Clinical Research Article

Incretin Hypersecretion in Gestational Diabetes Mellitus

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Abstract

Context: Incretins are crucial stimulators of insulin secretion following food intake. Data on incretin secretion and action during pregnancy are sparse.

Objective: The aim of the study was to investigate the incretin response during an oral glucose tolerance test (OGTT) in pregnant women with and without gestational diabetes mellitus (GDM).

Design: We analyzed data from the ongoing observational PREG study (NCT 04270578).

Setting: The study was conducted at the University Hospital Tübingen.

Participants: We examined 167 women (33 with GDM) during gestational week 27 ± 2.2.

Intervention: Subjects underwent 5-point OGTT with a 75-g glucose load.

Main outcome measures: We assessed insulin secretion and levels of total glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic peptide (GIP), glicentin, and glucagon during OGTT. Linear regression was used to analyze the relation of GLP-1 and glucose with insulin secretion and the association of incretin levels on birth outcome.

Results: Insulin secretion was significantly lower in women with GDM ($P < 0.001$). Postload GLP-1 and GIP were ~20% higher in women with GDM (all $P < 0.05$) independent of age, body mass index, and gestational age. GLP-1 increase was associated with insulin secretion only in GDM, but not in normal glucose tolerance. Postprandial GLP-1 levels were negatively associated with birth weight.

Conclusions: The more pronounced GLP-1 increase in women with GDM could be part of a compensatory mechanism counteracting GLP-1 resistance. Higher GLP-1 levels might be protective against fetal overgrowth.

Key Words: GDM, incretins, GLP-1, birth weight

Abbreviations: AUC, area under the curve; BMI, body mass index; DPP-4, dipeptidyl peptidase IV; GDM, gestational diabetes mellitus; GIP, glucose-dependent insulinotropic peptide; GLP-1, glucagon-like peptide-1; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test

Gestational diabetes mellitus (GDM) affects 13% of pregnancies with increasing incidence. In pregnancy, insulin resistance develops during the second trimester and is normally compensated for by an increase in insulin secretion (1). However, if this compensatory increase in insulin secretion falls short, glucose levels rise and GDM develops. When insulin resistance is resolved after delivery, glucose rapidly normalizes. Nevertheless, women who had GDM are at risk of subsequently developing type 2 diabetes (2).

Following food intake, specialized cells in the gastrointestinal tract release incretin hormones. The most thoroughly investigated incretins are glucagon like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). GLP-1 is cleaved from its precursor proglucagon along with other peptides, including glicentin and oxyntomodulin. Proglucagon gene products in pancreatic α cells give rise to glucagon.

GLP-1 and GIP are strong enhancers of glucose-stimulated insulin secretion. This incretin effect is reduced in type 2 diabetes and GDM (3).

However, only a few studies have investigated GLP-1 and GIP concentrations in GDM and reported contrasting results (4-7). One study investigating glucagon detected higher fasting and postglucose-challenge concentrations in GDM (8). No studies on glicentin in pregnancy have been published to date.

Objective

The aim of our study was to investigate the response of incretins and glucagon during an oral glucose tolerance test

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(OGTT) in pregnancy in a large cohort of well phenotyped women with normal glucose tolerance and GDM using precise preanalytics and specific immunoassays.

Materials and Methods

Subjects

We analyzed data from an ongoing study that aims to characterize metabolic alterations during pregnancy (PREG-Study): a cohort study recruiting women to undergo oral glucose tolerance tests for screening of GDM (NCT04270578). Pregnant women were examined between gestational week 24 + 0 and 31 + 6 with a 2-hour OGTT with 75 g glucose. GDM was diagnosed using the International Association of the Diabetes and Pregnancy Study Groups criteria (9) and patients were subsequently treated in accordance with national guidelines, albeit this was not part of the study. The detailed study protocol has already been described elsewhere (10). Written informed consent was obtained from every study participant. The study protocol was approved by the local ethics boards and the study was conducted in accordance with the Declaration of Helsinki. Patients were not involved in the design of the study. Follow-up meetings between study participants and researchers are held annually.

OGTT, Laboratory Analyses, and Anthropometric Assessment

Following an overnight fasting period of 12 hours, all study participants underwent 5-point OGTT with 75 g of glucose. Venous blood was collected at fasting and after 30, 60, 90, and 120 minutes. Plasma glucose and nonesterified fatty acids were measured from sodium-fluoride plasma in an ADVIA chemistry XPT autoanalyzer (Siemens Healthcare Diagnostics) at all timepoints. Serum insulin and C-peptide were analyzed using ADVIA Centaur XPT immunoassay system (Siemens AG) at all timepoints. For the measurement of total GIP, total GLP-1, glicentin, and glucagon EDTA-plasma from timepoint 0, 30, and 120 minutes was stabilized with 300 ng/mL of the protease inhibitor aprotinin (Sigma, Merck, Germany) und subsequently processed at 4°C and kept frozen at -80°C until batch measurement. Incretins and glucagon were measured with commercially available ELISA assays (Mercodia, Sweden, antibody IDs AB_2892202, AB_2895085, AB_2884906, and AB_2737304) in accordance with the manufacturer's instructions. High-sensitivity IL-6 was measured with ELISA (Human IL-6 Quantikine HS ELISA Kit, R&D Systems Minneapolis, MN, USA; antibody ID AB_2893335). Height and weight were measured at the day of OGTT. Pregestational weight, parity, gestational age at birth, and birthweight were obtained from maternal medical logs. Birth outcome data were available from 135 participants. Insulin sensitivity was calculated using the nonesterified fatty acid insulin sensitivity index (11). Insulin secretion was assessed with $\frac{AUC_{C-peptide\ 0-30}}{AUC_{Glucose\ 0-30}}$ and with ΔC-peptide$_{0\text{-}30}$, where AUC is area under the curve.

Statistical Analysis

All statistical analyses were performed with R Version 3.6.1. Continuous variables were tested for normal distribution using the Shapiro-Wilk test and transformed to natural logarithms to approximate normal distribution in multivariable linear regression models where necessary. Group differences were tested with *t* tests for normally distributed variables, Kruskal-Wallis test for non-normally distributed variables, and χ^2 test for categorical variables. The provided β coefficients are standardized estimates of the linear regression model terms. A P value < 0.05 was considered statistically significant.

Results

We analyzed data from 167 women, in 33 of whom GDM was diagnosed. Patients with GDM were older and more likely to be multiparous, but their body mass index (BMI) did not differ from women with normal glucose tolerance (NGT; Table 1).

Glucose and Hormones During OGTT

Insulin secretion and sensitivity were lower in GDM (Fig. 1A and 1B). AUCs of glucose and C-peptide were higher in GDM (Fig. 1C and 1D). Although fasting levels of GLP-1 and GIP were similar, the levels at 30 minutes were higher in GDM (Table 2). The AUCs of GLP-1 and GIP were also higher in GDM (all $P < 0.05$; Fig. 1E and 1F, Table 2). Fasting glicentin, glucagon, and their postload kinetics did not differ between groups ($P \geq 0.1$; Fig. 1G and 1H, Table 2).

GLP-1 Associates With Insulin Secretion Only in Women With GDM

We hypothesized that higher incretin levels in GDM represent a compensatory effect to boost insulin secretion. We therefore analyzed the associations of GLP-1 and glucose with insulin secretion (Figure S1 (12)). In NGT, increase in glucose between 0 and 30 minutes was associated with insulin secretion (Figure S1A, $P < 0.0001$ (12)). No such association was present for GLP-1 (Figure S1B, $P = 0.43$ (12)).

By contrast, women with GDM showed no association of glucose (Figure S1C, $P = 0.6$ (12)) but a positive association of GLP-1 with insulin secretion (Figure S1D, $P = 0.0004$ (12)). This remained significant after adjustment for glucose change and basal insulin. Glicentin was similarly associated with insulin secretion in GDM and NGT (Figure S2 (12)). For GIP, there was no association with insulin secretion (Figure S3 (12)).

Incretin Hypersecretion Is Not Mediated by IL-6

To address IL-6 as a potential mediator of an increased incretin response in GDM, we analyzed its association with fasting GLP-1 and GLP-1 secretion during OGTT. IL-6 was associated with fasting GLP-1 ($P = 0.03$, $\beta = 0.1$), but this was attenuated after adjustment for age, BMI, and gestational age. There was no association with stimulated GLP-1 levels ($P = 0.45$, linear regression model adjusted for BMI, fasting GLP-1, and gestational age). Likewise, no association with postchallenge GIP was observed ($P = 0.44$). For glicentin, there was a trend toward a negative association ($P = 0.052$, $\beta = -0.2$).

Higher GLP-1 Associates With Lower Birth Weight

In the whole cohort, birth weight was negatively associated with AUC GLP-1 ($P = 0.0182$, $\beta = -76.94$) and 30-minute GLP-1 ($P = 0.0248$, $\beta = -72.6$) and it showed a trend toward a negative association with 30-minute GIP ($P = 0.0814$, $\beta = -57.45$, all models adjusted for gestational age at birth,

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Table 1. Subject characteristics of the pregnant cohort and birth outcome parameters

Characteristics	NGT (n = 134)	GDM (n = 33)	*P*	$P_{adjusted}$
Age	32.71 (4.31)	35.03 (3.84)	0.005[a]	-
BMI, kg/m^2	26.90 [23.97, 29.94]	26.90 [24.72, 30.99]	0.497	-
Pregestational BMI, kg/m^2	25.37 (5.25)	25.50 (4.96)	0.906	-
Gestational weight gain, kg	14.06 (5.53)	11.46 (7.10)	0.085	-
Parity, %				
Nulliparous	69 (51.5)	9 (27.37)	0.021[a]	-
Multiparous	65 (48.5)	24 (72.7)		
Gestational age at OGTT, wk	26.87 (2.16)	27.27 (2.11)	0.332	-
Fasting glucose, mmol/L	4.28 [4.07, 4.54]	4.56 [4.33, 4.94]	<0.001[a]	-
1-h glucose, mmol/L	7.70 [6.40, 8.56]	10.61 [9.56, 11.33]	<0.001[a]	-
2-h glucose, mmol/L	6.11 [5.34, 6.83]	8.83 [7.72, 9.44]	<0.001[a]	-
Fasting insulin, pmol/L	59 [42, 79]	69[41, 84]	0.460	-
Fasting C-peptide, pmol/L	381.50 [296.50, 496.50]	466.00 [282.00, 652.00]	0.150	-
IL-6, pg/mL	0.65 [0.41, 1.05]	0.88 [0.63, 1.25]	0.037[a]	0.23[b]
Insulin sensitivity, nonesterified fatty acid insulin sensitivity index	3.34 [2.56, 4.39]	2.72 [2.01, 4.26]	0.031[a]	0.003[a,b]
Insulin secretion, $AUC_{C\text{-}pep\ 0\text{-}30}/_{AUCGlucose0\text{-}30}$	179.22 (60.12)	155.17 (54.53)	0.037[a]	<0.001[a,c]
Birth weight, g[d]	3478.18 (479.84)	3321.52 (384.38)	0.084	0.24[e]
Birth length, cm[d]	51.48 (2.37)	50.48 (2.68)	0.042	0.27[e]
Gestational age at birth, wk	39.51 (1.59)	39.16 (1.17)	0.240	-

Data are presented as means (SD), median [interquartile ratio], and numbers (%). Group differences were tested with *t* test for normally distributed variables, Kruskal-Wallis test for non-normally distributed variables, and χ^2 test for categorical variables.
Abbreviations: AUC, area under the curve; BMI, body mass index; GDM, gestational diabetes mellitus; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test.
[a]Indicates statistical significance.
[b]Adjusted for age, BMI, and gestational age.
[c]Adjusted for age, BMI, gestational age, and insulin sensitivity.
[d]n = 135.
[e]Adjusted for gestational age and fetal sex.

fetal sex, and pregestational BMI). Because GLP-1 and GIP concentrations were higher in GDM, the models were additionally adjusted for GDM. Associations of birth weight with AUC GLP-1 and 30-minute GLP-1 remained significant ($P = 0.0296$, $\beta = -72.43$, and $P = 0.0381$, $\beta = -68.49$, respectively). Furthermore, these associations also remained significant after adjusting for glycemia (1-hour glucose [AUC GLP-1: $P = 0.0193$, $\beta = -77.78$; 30-minute GLP-1: $P = 0.0221$, $\beta = -75.95$] and 2-hour glucose, respectively [AUC GLP-1: $P = 0.0247$, $\beta = -74.77$; 30-minute GLP-1: $P = 0.0263$, $\beta = -73.55$]).

Discussion

Main Findings

In this study, we found significantly higher postprandial GLP-1 and GIP levels in pregnant women with GDM compared with women with NGT, independent from age, BMI, and gestational age. The postprandial GLP-1 increase was associated with insulin secretion in women with GDM but not in women with NGT, in whom insulin secretion was glucose driven. Offspring of women with higher GLP-1 levels also had lower birth weights.

Interpretation

GLP-1 and GIP have previously been investigated in women with and without GDM in smaller studies with different results (4, 6, 7, 13). One study used a different stimulus (mixed meal test) (6), and large BMI differences (6, 13) between NGT and GDM subjects might have further confounded the analyses because BMI negatively associates with GLP-1 and GIP (14). In our study, participants with and without GDM had similar BMI, enabling us to make a direct assessment of GDM on incretin response, without adiposity as confounding factor.

Intestinal L-cells also secrete glicentin, a potential biomarker of L-cell secretion (15). The lack of difference in glicentin between NGT and GDM argues against an unselective L-cell hypersecretion in GDM.

In contrast to findings on glucagon outside of pregnancy (16), we and others (6) did not detect an association of glucagon levels with glycemic endpoint during pregnancy. Although this argues against a major contribution of glucagon in the pathogenesis of GDM, it might have some value in predicting insulin requirement for the treatment of GDM (17).

Of note, women with GDM had a lower insulin secretion despite higher GLP-1 and GIP concentrations. Our correlational analyses indicate an important contribution of GLP-1 to insulin secretion, especially in GDM. However, this GLP-1 stimulus is still not sufficient to control hyperglycemia. The failure of adequate insulin secretion despite elevated GLP-1 indicates incretin resistance in GDM. A more pronounced GLP-1 response in GDM could be counteracting incretin resistance. Incretin resistance, in turn, is associated with the combination of insulin resistance and hyperglycemia, which is characteristic of GDM (18).

The mediator of higher GLP-1 levels, however, remains unknown. The inflammatory cytokine IL-6 stimulates GLP-1

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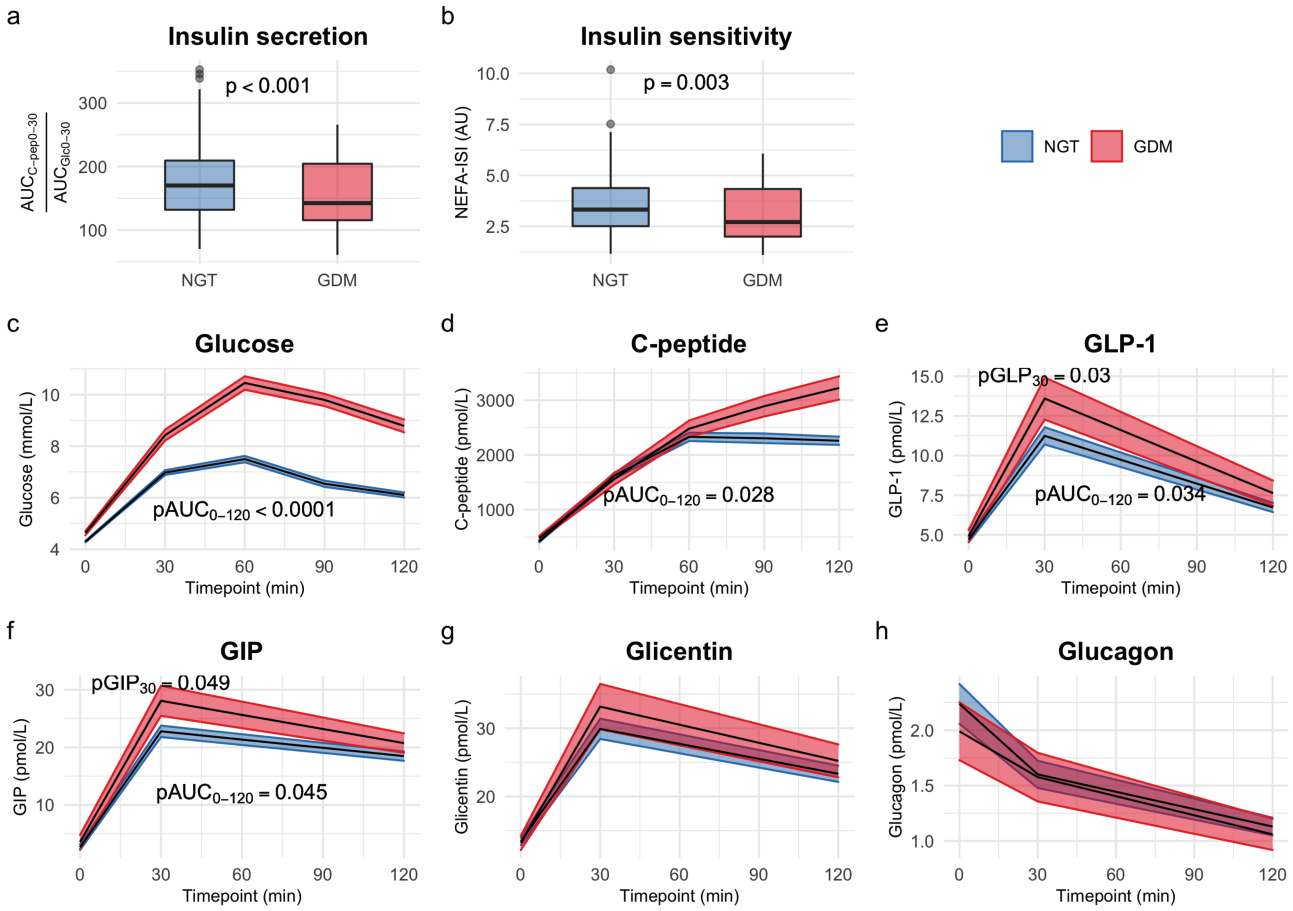

Figure 1. Insulin secretion (A) and insulin sensitivity (B) in women with and without GDM and time course of glucose (C), C-peptide (D), GLP-1 (E), GIP (F), glicentin (G), and glucagon (H) during OGTT. Data are presented as mean ± standard error. Blue represents NGT, red GDM. Group differences between GDM and NGT for AUCs of glucose, insulin, and C-peptide were tested using the Kruskal-Wallis test. Differences in insulin sensitivity, incretins, and glucagon between the groups were tested with multivariate linear regression which was adjusted for age, BMI, and gestational week. Differences in insulin secretion were additionally adjusted for insulin sensitivity.

Table 2. Incretin concentrations during OGTT and AUCs in the pregnant cohort

Incretin	NGT (n = 134)	GDM (n = 33)	*P*	$P_{adjusted}$ [a]
GLP-1 min 0 (pmol/L)	4.48 [3.42, 5.53]	4.83 [3.56, 6.18]	0.393	0.6
GLP-1 min 30 (pmol/L)	9.89 [7.10, 12.83]	11.31 [8.65, 14.98]	0.034[b]	0.03[b]
GLP-1 min 120 (pmol/L)	5.71 [4.55, 8.27]	6.48 [5.05, 9.30]	0.175	0.3
AUC GLP-1 (min/pmol/L)	911.19 [726.59, 1207.49]	1136.24 [913.21, 1342.74]	0.03[b]	0.03[b]
GIP min 0 (pmol/L)	0.81 [0.81, 1.50]	0.81 [0.81, 1.76]	0.312	0.5
GIP min 30 (pmol/L)	20.21 [14.12, 29.69]	24.12 [18.76, 35.77]	0.049[b]	0.02[b]
GIP min 120 (pmol/L)	17.48 [11.92, 23.58]	19.20 [14.96, 27.13]	0.191	0.1
AUC GIP (min/pmol/L)	2022.49 [1421.28, 2887.34]	2532.15 [1899.17, 3219.01]	0.045[b]	0.04[b]
Glicentin min 0 (pmol/L)	12.37 [8.53, 16.92]	12.59 [9.56, 16.56]	0.989	0.9
Glicentin min 30 (pmol/L)	25.10 [19.26, 34.73]	28.33 [25.16, 35.13]	0.122	0.1
Glicentin min 120 (pmol/L)	20.17 [14.97, 30.45]	21.66 [14.44, 29.84]	0.602	0.3
AUC Glicentin (min/pmol/L)	2715.75 [2092.97, 3529.69]	2912.80 [2426.76, 3574.03]	0.198	0.1
Glucagon min 0 (pmol/L)	1.45 [0.81, 3.42]	1.43 [0.95, 2.96]	0.873	0.6
Glucagon min 30 (pmol/L)	1.35 [0.55, 2.20]	1.15 [0.78, 2.54]	0.550	0.4
Glucagon min 120 (pmol/L)	0.91 [0.44, 1.53]	0.74 [0.46, 1.50]	1.000	0.9
AUC glucagon (min/pmol/L)	139.11 [74.68, 236.32]	124.74 [89.05, 262.70]	0.659	0.9

Data are presented as median [IQR]. Simple group differences were tested with Kruskal-Wallis test.
Abbreviations: AUC, area under the curve; BMI, body mass index; GDM, gestational diabetes mellitus; GIP, glucose-dependent insulinotropic peptide; GLP-1, glucagon-like peptide-1; OGTT, oral glucose tolerance test.
[a]Adjusted for age, BMI, and gestational week.
[b]Indicates statistical significance.

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secretion (19) and we observed higher IL-6 levels in the GDM group. Beyond a positive association with fasting GLP-1, we did not detect an association of IL-6 with stimulated incretin levels in our data. Thus, this cytokine has likely no major contribution to the current findings. Another possible contributor might be dipeptidyl peptidase IV (DPP-4) activity, the enzyme degrading GLP-1 and GIP. Liu et al (20) reported no differences of DPP-4 in maternal serum. In line with this, the unaltered fasting GLP-1 levels in GDM in our study argue against largely different DPP-4 activity with regard to GDM.

Genetic background, specifically variants of the *TCF7L2* gene, might play a role in incretin resistance. The rs7903146 polymorphism in *TCF7L2* is associated with a reduced insulinotropic effect of GLP-1 (18) and a higher GDM risk (21). This genetically determined incretin resistance may partly explain the differences between non-GDM and GDM participants in GLP-1 response, however, our study was not adequately powered for detailed genetic analyses. Other genetic and nongenetic factors could certainly also contribute to a heterogeneity of incretin response. Unfortunately, however, the molecular pathways underlying this phenomenon are still elusive.

In our study, neonates born to women with higher GLP-1 levels during pregnancy had lower birth weight, independent of glycemia. This suggests that GLP-1 protects against excessive fetal growth. Our findings are in line with a report of negative association between fasting maternal GLP-1 and fetal abdominal circumference and birth weight (22). Higher GLP-1, also via decelerated gastric emptying, might reduce the postprandial glucose, which is associated with fetal overgrowth. If this hypothesis holds true, GLP-1 receptor agonists or DPP-4 inhibitors might have benefits in GDM. To our knowledge, no studies are currently involved in testing GLP-1R agonists in GDM. One trial reported higher insulin secretion after 16 weeks of treatment with the DPP-4 inhibitor sitagliptin in GDM (23). However, neither incretins nor birth outcomes were reported.

Strengths and Limitations

The strength of our study is the large number of subjects of our extensively phenotyped cohort of pregnant women. The sample preparation and measurement of incretins was carried out in accordance with standard operating procedures and with state-of-the-art measuring methods. One weakness is the relatively low number of patients with GDM.

Conclusion

In summary, elevated GLP-1 could be part of a compensatory attempt to counteract GLP-1 resistance in GDM. Higher GLP-1 levels might protect against fetal overgrowth. Our data suggest that not only glucose-stimulated but also incretin-stimulated insulin secretion contributes to GDM. Further studies are required to translate these findings into improved therapeutic strategies to prevent or treat GDM and to circumvent unfavorable impact on the developing child.

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Author Contributions

L.F. researched and analyzed data and drafted the manuscript. J.H., S.N., and R.W. researched data. H.U.H., A.L.B., H.P., A.S., and A.F. contributed to the discussion and interpretation of the results. A.P. supervised the laboratory measurements and interpreted results. R.W. and M.H. supervised the project. All authors contributed to discussion and approved the final manuscript before submission. R.W. is the guarantor of this work and, as such, had full access to all the data in the study and assumes responsibility for the integrity of the data and the accuracy of the data analysis.

Disclosures

R.W. reports lecture fees from NovoNordisk and travel grants from Eli Lilly and he served on the advisory board of Akcea Therapeutics. In addition to his current work, A.L.B. reports lecture fees from Astra Zeneca, Boehringer Ingelheim, and NovoNordisk and serving on advisory boards of Astra Zeneca, Boehringer Ingelheim, and NovoNordisk. Besides his current work, A.F. reports lecture fees and advisory board membership from Sanofi, Novo Nordisk, Eli Lilly, and AstraZeneca. In addition to his current work, M.H. reports research grants from Boehringer Ingelheim and Sanofi (both to the University Hospital of Tuebingen) and lecture fees from Sanofi, Novo Nordisk, Eli Lilly. and Merck Sharp Dohme; he has served on an advisory board of Boehringer Ingelheim. None of the other authors report a conflict of interest directly related to the content of this work.

Data Availability

All requests for data and materials will be promptly reviewed by the Data Access Steering Committee to verify whether the request is subject to any intellectual property or confidentiality obligations. Individual-level data may be subject to confidentiality. Any data and materials that can be shared will be released via a Material Transfer Agreement.

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