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Glucometabolic Alterations in Pregnant Women with Overweight or Obesity but without Gestational Diabetes Mellitus: An Observational Study

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Keywords
Glucose metabolism · Obesity · Pregnancy · Intravenous glucose tolerance test

Abstract
Introduction: Maternal overweight is a risk factor for gestational diabetes mellitus (GDM). However, emerging evidence suggests that an increased maternal body mass index (BMI) promotes the development of perinatal complications even in women who do not develop GDM. This study aims to assess physiological glucometabolic changes associated with increased BMI. ***Methods:*** Twenty-one women with overweight and 21 normal weight controls received a metabolic assessment at 13 weeks of gestation, including a 60-min frequently sampled intravenous glucose tolerance test. A further investigation was performed between 24 and 28 weeks in women who remained normal glucose tolerant. ***Results:*** At baseline, mothers with overweight showed impaired insulin action, whereby the calculated insulin sensitivity index (CSI) was lower as compared to normal weight controls (3.5 vs. 6.7 10^{-4} min^{-1} $[microU/mL]^{-1}$, p = 0.025). After excluding women who developed GDM, mothers with overweight showed higher average glucose during the oral glucose tolerance test (OGTT) at the third trimester. Moreover, early pregnancy insulin resistance and secretion were associated with increased placental weight in normal glucose-tolerant women. ***Conclusion:*** Mothers with overweight or obesity show an unfavorable metabolic environment already at the early stage of pregnancy, possibly associated with perinatal complications in women who remain normal glucose tolerant.

Introduction

The prevalence of overweight and obesity is increasing in reproductive-aged women and is closely associated with complications during pregnancy and adverse pregnancy outcomes [1]. This may be in part explained by a strong coincidence between increased body mass index (BMI) and gestational diabetes mellitus (GDM) [2, 3]. However, emerging evidence suggests that maternal

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overweight or obesity can impact the development of the offspring also in women without a diagnosis of GDM [4]. For example, a secondary analysis of the Hyperglycaemia and Adverse Pregnancy Outcomes (HAPO) study showed that elevated maternal BMI was related to fetal adiposity, pre-eclampsia, and increased frequency of caesarean section independently of maternal glycemia [5]. In addition, previous studies indicated an increased risk of stillbirth in women with extreme obesity [6], whereas no association between maternal dysglycemia and perinatal mortality was observed in the HAPO study [7].

The underlying pathophysiologic pathways mediating the link between increased maternal BMI and adverse pregnancy outcomes are not well understood. Metabolic alterations associated with increased maternal body weight, such as impaired insulin action and hyperinsulinemia at the beginning of pregnancy, possibly affect the fetoplacental unit to increase nutrient supply, thus promoting fetal overgrowth [1]. Moreover, the well-known association between insulin resistance and endothelial dysfunction [8] may be responsible for the higher rate of prenatal complications and, therefore, the risk of caesarean section observed in mothers with obesity [9]. Consequently, a more detailed description of the metabolic environment at the beginning of pregnancy is necessary to clarify the mechanisms linking elevated maternal BMI and adverse obstetric outcomes.

For this purpose, the present study aimed to assess the metabolic changes associated with maternal overweight or obesity. Parameters of impaired insulin action and secretion as well as serum lipids were assessed at early pregnancy. Glucose and insulin metabolism were re-evaluated at mid-gestation in women who remained normal glucose tolerant (NGT) to describe possible subtle metabolic alterations occurring in mothers with an increased BMI who were not diagnosed with GDM.

Material and Methods

Study Design and Participants

A total of 42 women (21 mothers with overweight or obesity (OW/OB) with pregestational BMI ≥25 kg/m^2 and 21 normal weight controls (CONT) with BMI <25 kg/m^2) were consecutively recruited in 2019 and 2020 at the pregnancy outpatient clinic (Department of Obstetrics and Gynecology, Medical University of Vienna, Vienna, Austria). The calculation of pregestational BMI was performed by self-reported pre-conceptional weight, which showed a high correlation with technician-measured weight in previous studies [10]. Study participants received a detailed metabolic assessment at 13.3 (interquartile range, IQR: 12.5–14.4) weeks of gestation (visit 1). This included an evaluation of patients' history, actual weight, height and waist circumference, as well as a blood examination of serum lipids at fasting state (triglycerides [TG], total cholesterol [TC], low-density lipoprotein and high-density lipoprotein [HDL] cholesterol), glycated hemoglobin A1c (HbA1c), C-reactive protein (CRP), and a short frequently sampled intravenous glucose tolerance test (IVGTT) after at least 8 h fasting. For the IVGTT, glucose (300 mg/kg body weight) was infused for 30 s starting at time 0 and normal insulin (0.03 IU/kg) from 20 to 25 min, respectively. Plasma concentrations of glucose, insulin, and C-peptide were assessed at fasting as well as at 0, 3, 4, 5, 6, 8, 10, 15, 20, 30, 40, 50, and 60 min. The patients were invited for a second examination at mid-gestation (median: 24.6, IQR: 24.3–24.9 weeks of gestation, visit 2). At this time, a 2 h–75 g oral glucose tolerance test (OGTT) was conducted. For this purpose, participating women received a 300-mL oral glucose load (75 g glucose solution) after fasting and blood sampling of glucose, insulin, and C-peptide. Further samples were taken at 30, 60, 90, and 120 min.

Calculation of Insulin Sensitivity and Beta Cell Function

The homeostasis model assessment of insulin resistance (HOMA-IR) and the quantitative insulin sensitivity check index (QUICKI) were used to assess insulin resistance (or sensitivity) from fasting parameters as an approximation of hepatic insulin action [11, 12]. The calculated insulin sensitivity index (CSI) was assessed from the IVGTT data, representing a reliable surrogate of clamp-derived whole-body insulin sensitivity [13]. Beta cell function from the IVGTT was assessed by the disposition index (DI), computed as the product of CSI and the mean incremental acute (short-term) insulin response to glucose from 3 to 10 min (dAIRG). In fact, DI is an expression of the ability of the pancreatic beta cells to adapt for impaired insulin sensitivity [14]. Average values of glucose, insulin, and C-peptide were used to summarize dynamic assessments during both the IVGTT and the OGTT.

Laboratory Analyses

Glucose was assessed by the hexokinase method with a coefficient of variation (CV) of 1.3% (101 mg/dL). Insulin (CV: 4–7%) and C-peptide (CV: 3–4%) were assessed by luminescence immunoassays. HbA1c was measured by high-performance liquid chromatography using Variant II, Bio-Rad, IFCC (International Federation of Clinical Chemistry) standardized, and DCCT (Diabetes Control and Complications Trial) aligned with a CV of 1.8%. All further laboratory parameters (including lipids and CRP) were measured according to the standard methods at the Department of Medical and Chemical Laboratory Diagnostics (http://www.kimcl.at).

Newborns' Anthropometry

Newborns' anthropometry and placental weight were assessed immediately after delivery. Calculations of age-adjusted and sex-adjusted percentiles of newborns' birth weight were based on local anthropometric standards.

Statistical Analysis

Continuous variables were summarized by means and standard deviations and compared by Welch's *t* test. In case of skewed distributed parameters, they were summarized by median and interquartile range and compared by rank-based inference (such as the Wilcoxon rank-sum test). Multivariable adjustments were performed by analysis of covariance or by use

Table 1. Characteristics of the study sample at study entrance (visit 1) in normal weight controls (CONT) and women with overweight or obesity (OW/OB)

	CONT (n = 21)	OW/OB (n = 21)	p value
Age, years	30.1±5.8	33.1±5.1	0.075
Parity	0 (0–1)	1 (0–2)	0.064
BMI, before pregnancy, kg/m^2	21.4±2.4	30.3±5.2	<0.001
BMI, initial contact, kg/m^2	21.8±2.3	30.5±5.5	<0.001
Waist circumference, cm	86.2±8.0	107.2±12.5	<0.001
Triglycerides, mg/dL	101±31	131±55	0.034
Total-cholesterol, mg/dL	185±30	192±33	0.426
LDL-cholesterol, mg/dL	90.8±25.7	96.7±26.5	0.476
HDL-cholesterol, mg/dL	73.6±11.7	69.4±14.5	0.316
CRP, mg/dL	0.42±0.27	0.78±0.56	0.013
HbA1c, %	4.90±0.28	5.20±0.35	0.004
F-G, mg/dL	80.9±4.9	88.2±8.4	0.002
F-I, µU/mL	8.86±4.34	14.13±8.80	0.021
F-CP, ng/mL	1.53±0.38	2.21±0.86	0.003
HOMA-IR (dimensionless)	1.79±0.91	3.15±2.41	0.024
QUICKIc (dimensionless)	0.48±0.04	0.44±0.03	0.001
IVGTT-G mean, mg/dL	153.3±23.6	177.3±24.8	0.004
IVGTT-I mean, µU/mL	58.13±33.95	77.28±39.27	0.111
IVGTT-CP mean, ng/mL	4.58±1.32	5.72±1.52	0.016
CSI (10^{-4} min^{-1} [µU/mL]$^{-1}$)	6.7 (4.4–15.0)	3.5 (2.1–6.7)	0.025
dAIRG, µU/mL	67.52±37.37	97.16±63.57	0.183
DI (CSI × dAIRG)	508 (271–802)	256 (174–483)	0.041

Data are mean ± standard deviation or median (interquartile range); BMI, body mass index; HbA1c, glycated hemoglobin A1c; F-G, fasting glucose, F-I, fasting insulin; F-CP, fasting C-peptide; CRP, C-reactive protein; HOMA-IR, homeostasis model assessment; QUICKIc, quantitative insulin sensitivity check index from C-peptide; IVGTT-G mean, mean glucose during IVGTT; IVGTT-I mean, mean insulin during IVGTT; IVGTT-CP mean, mean C-peptide during IVGTT; CSI, calculated insulin sensitivity index; dAIRG, acute insulin response to glucose calculated on the basis of insulin secretion; DI, disposition index from insulin; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

of the proportional odds model, respectively. Bivariate associations between ordinal and metric scaled variables were assessed by Spearman's correlation, and associations with dichotomous dependent variables were assessed by binary logistic regression, which was used to estimate odds ratios (OR) and 95% confidence intervals (95% CI) by the likelihood ratio statistic. Statistical analysis was performed by R (V. 4.2.2) and contributing packages. The two-sided significance level was set to 0.05. However, p values were interpreted in an explorative manner, and there was no further adjustment for multiplicity if not otherwise indicated in the manuscript.

Results

Patient Characteristics and Metabolic Profile at the Initial Contact (Visit 1)

Table 1 shows the characteristics of study participants at visit 1. As compared to normal weight controls, mothers with overweight or obesity showed increased HbA1c as well as fasting glucose, insulin, and C-peptide concentrations. This was associated with impaired "hepatic" (i.e., fasting) parameters of insulin action (i.e., HOMA-IR and QUICKI). Moreover, dynamically assessed "whole body" insulin sensitivity (CSI) was decreased in mothers with elevated BMI, who also showed higher average levels of C-peptide during the IVGTT. However, the lower disposition index indicated that subtle impairments in beta cell function in women with overweight or obesity were already present at the beginning of pregnancy (Fig. 1). Likewise, parameters of maternal anthropometry were positively associated with fasting glucose, insulin, C-peptide, insulin resistance (fasting and dynamically assessed) as well as with elevated triglycerides and CRP concentrations, whereas no association was observed with cholesterol levels at the initial contact

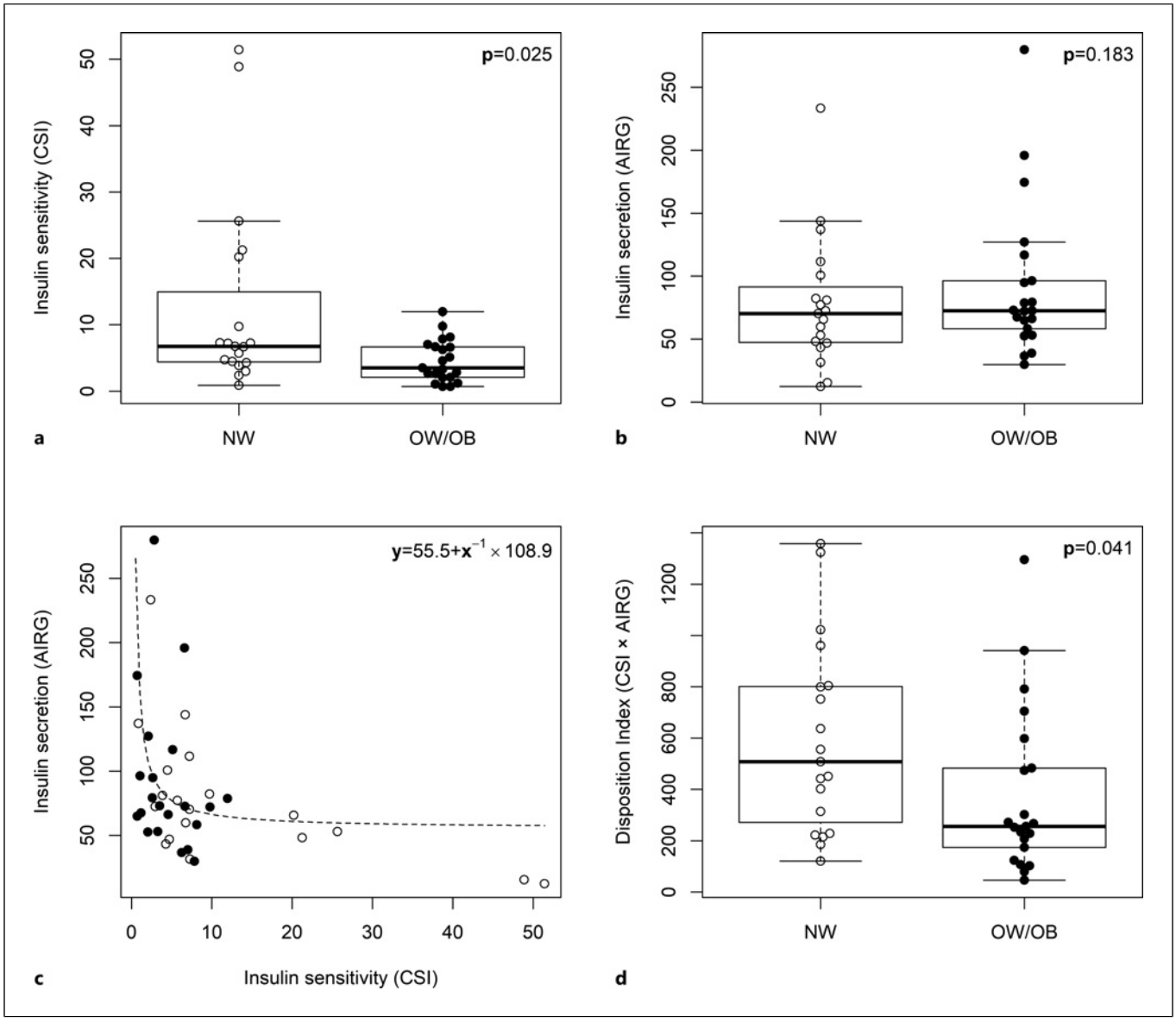

Fig. 1. a Whole-body insulin sensitivity (CSI). **b** Acute insulin response to glucose from insulin (dAIRG). **c** Relationship between dAIRG and insulin sensitivity. **d** Boxplot of disposition index from insulin. White dots: normal weight; black dots: overweight or obese.

(Fig. 2a). Moreover, a significant negative association was found between maternal BMI, WC, and beta cell function.

Association of Metabolic Profile at Early Gestation with GDM Development

A total of 6 women were diagnosed with GDM in our cohort. This was associated with glucometabolic parameters at early gestation, such as fasting glucose (OR: 1.58, 95% CI: 1.20–2.54, $p < 0.001$, for the increase of 1 mg/dL), maternal insulin sensitivity (CSI: OR 2.23, 95% CI: 1.29–5.47, $p < 0.001$), and beta-cell function (DI: OR 1.02, 95% CI: 1.01–1.04, $p < 0.001$), representing the relative increase in the odds for developing GDM, if insulin sensitivity (CSI) or beta cell function (DI) is decreased by 1 unit, whereas a tendency was observed between pregestational BMI and GDM status ($p = 0.075$).

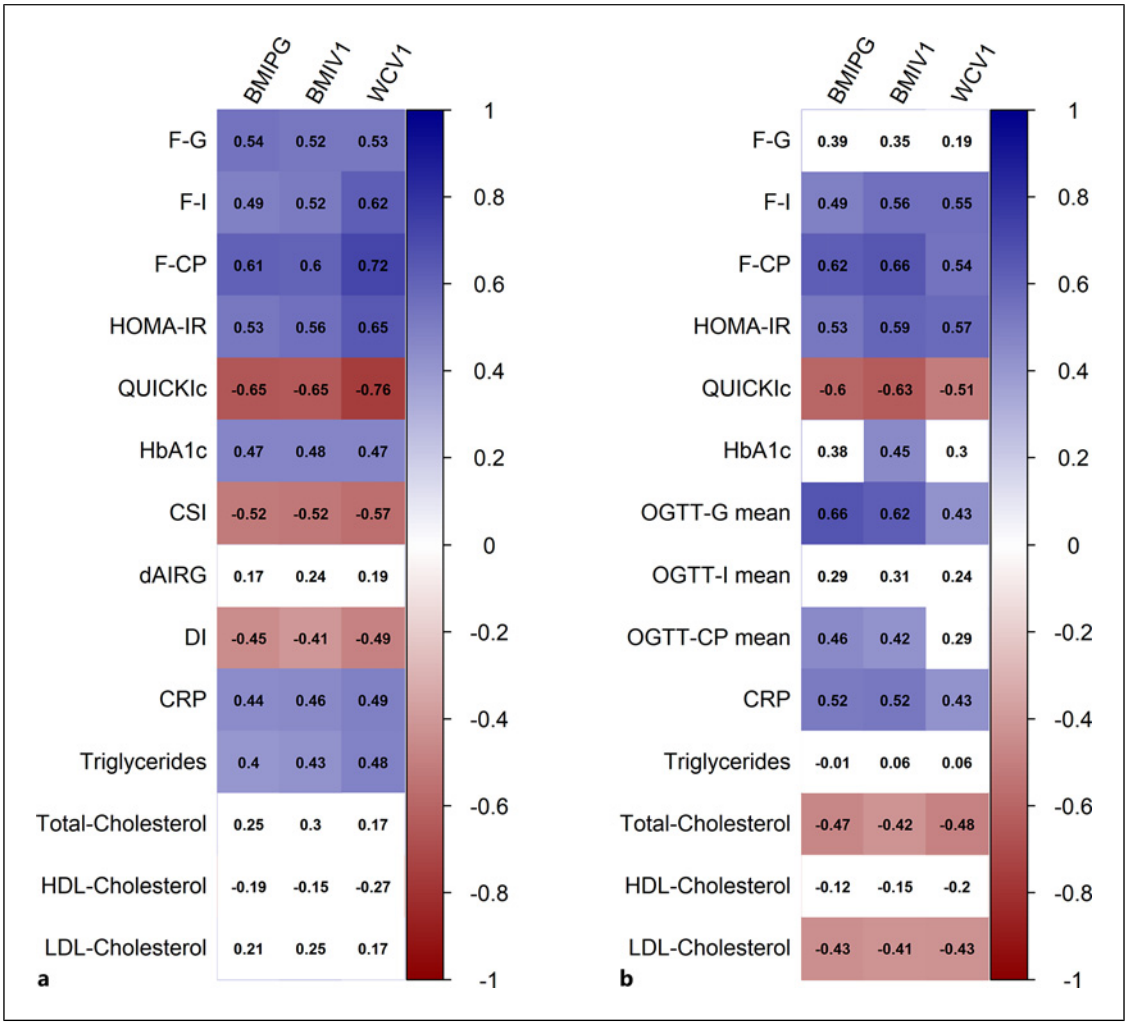

Fig. 2. Heat-map representing the association between pregestational BMI (BMIPG) as well as BMI (BMIV1) and waist circumference (WCV1) at the initial contact with parameters of glucose metabolism at the baseline examination (V1, **a**) as well as between 24 and 28 weeks of gestation (V2, **b**) in women who remained NGT. For significant associations ($p < 0.05$), the amount of correlation is indicated by the color from bright (weak correlation) to dark (strong correlation), whereby blue color indicates positive and red color indicates negative associations. The number is Spearman's rank correlation coefficient.

Metabolic Profile at Mid Gestation in Women Who Did Not Develop GDM (Visit 2)

After excluding women who developed GDM, mothers with overweight or obesity showed higher average glucose (101 ± 13 vs. 115 ± 16 mg/dL, $p = 0.027$) and C-peptide levels (median 6.88, IQR: 5.32–7.10 vs. 8.52, IQR: 7.24–8.84 ng/dL, $p = 0.029$) during the OGTT (Fig. 3). However, the observed differences in glucose concentrations were attenuated after adjustment for maternal beta cell function at start of pregnancy (CONT vs. OW/OB, $p = 0.108$), whereas the DI at the first visit remained significantly associated with higher glucose concentrations ($p < 0.001$). A complete picture of the associations between maternal biometric measures at the initial contact and metabolic parameters at visit 2 is shown in Figure 2b. Maternal anthropometry was positively associated with mean glucose and C-peptide levels during the OGTT as well as with CRP and fasting insulin resistance, whereas a significant negative association was observed between maternal BMI and TC as well as low-density lipoprotein. Gestational weight gain was comparable between controls and mothers with overweight or obesity (8.5 ± 5.5 vs. 8.9 ± 4.3 kg, $p = 0.834$).

Associations with Offspring and Placenta Weight

Birth weight percentiles did not significantly differ between normal glucose-tolerant mothers with normal weight and those with overweight or obesity (34.9 ± 25.2 vs. 38.7 ± 22.1, $p = 0.634$). However, we observed that placenta weight (which was available in 33 cases) was inversely associated with insulin sensitivity (CSI: rho = −0.43, $p = 0.016$) and positively associated with insulin secretion (dAIRG: rho = 0.53, $p = 0.002$) as well as average C-peptide concentrations (rho = 0.53, $p = 0.002$) during the IVGTT at early pregnancy, but not with beta cell function ($p = 0.892$), pregestational BMI ($p = 0.465$), or average glucose concentrations ($p = 0.498$). In a further analysis, we could not identify an association between maternal GDM status and birth weight percentiles ($p = 0.119$) or placenta weight ($p = 0.119$), although these results may be limited due to the small number of available cases.

Discussion

This study aimed to assess metabolic alterations associated with maternal overweight or obesity and found that elevated maternal BMI was closely associated with altered parameters of glucose metabolism already in the early stages of pregnancy. A detailed glucometabolic assessment at the end of the first trimester revealed markedly impaired insulin action and slightly elevated insulin secretion. However, in contrast to normal-weight women, the increase in insulin release was not able to fully compensate for the decrease in insulin sensitivity. This is reflected by a lower disposition index associated with elevated BMI, hinting towards alterations in beta cell functionality already in early pregnancy of mothers with overweight or obesity, which was closely associated with an increased risk for developing GDM. Maternal pregestational BMI was not predictor for the later development of GDM in this study cohort. However, the number of patients developing GDM was only 6, resulting in an incidence of 14.29%, which is comparable to the incidence reported for Middle European countries of approximately 11% [15]. Moreover, the gestational weight gain of mothers with overweight or obesity was comparable to normal weight controls in this study cohort. However, pregestational overweight or obesity is a risk factor for excessive gestational weight gain [16], and both conditions, pre-gestationally elevated BMI and gestational weight gain, have additive negative effects on maternal and neonatal pregnancy outcomes [17].

Women affected by overweight or obesity, who remained NGT (i.e., were not diagnosed with GDM according to IADPSG criteria later in pregnancy), nonetheless showed higher average glucose and C-peptide levels during the diagnostic OGTT at later pregnancy as compared to normal-weight mothers. This, however, can possibly rather be explained by early pregnancy beta cell dysfunction (i.e., lower disposition index) than by overweight or obesity status per se.

The results of this study are supported by previous investigations, suggesting a close association between maternal obesity and impaired insulin sensitivity [18], probably triggered by subclinical inflammation [19, 20]. Supposedly, dysfunctional hypertrophic adipocytes secrete proinflammatory cytokines, which directly interfere with intracellular insulin signaling pathways. Also, excessive amounts of free fatty acids are secreted which increase ectopic lipid accumulation and lipotoxic effects in organs such as the liver, muscle, and heart [21, 22].

In contrast to this well-known link between obesity and insulin resistance, the association between obesity and impaired beta cell functionality is less well investigated or understood. Some studies have observed pancreatic islet inflammation in subjects with obesity associated with an increase in islet-resident macrophages which absorb insulin-secretory granules [23, 24]. Although we have not specifically assessed inflammation parameters, patients with overweight or obesity in this study had significantly higher CRP levels as compared to normal weight controls already at the start of gestation.

In women affected by overweight or obesity, an unfavorable metabolic profile exists even before conception, leading to an altered glucometabolic environment at the beginning of pregnancy, as shown in this study. As pregnancy progresses, a physiological decrease in insulin sensitivity of up to 80% occurs [25], requiring a compensatory increase in insulin secretion [26]. Consequently, even subtle alterations in beta cell function in patients with obesity (as shown in this study) may lead to the later development of GDM. Interestingly, mothers with overweight or obesity who did not develop GDM in this study cohort nonetheless showed a significantly different metabolic profile during the diagnostic OGTT at the beginning of the third trimester with significantly higher mean glucose and C-peptide values as compared to normal weight controls. This is in line with another study finding significantly higher glycemic levels in obese NGT patients compared to normal weight controls by using real-time continuous glucose monitoring (rt-CGM) [27]. These findings may contribute to the observation that even in the absence of GDM, mothers with obesity seem to have a higher risk of large for gestational age infants as

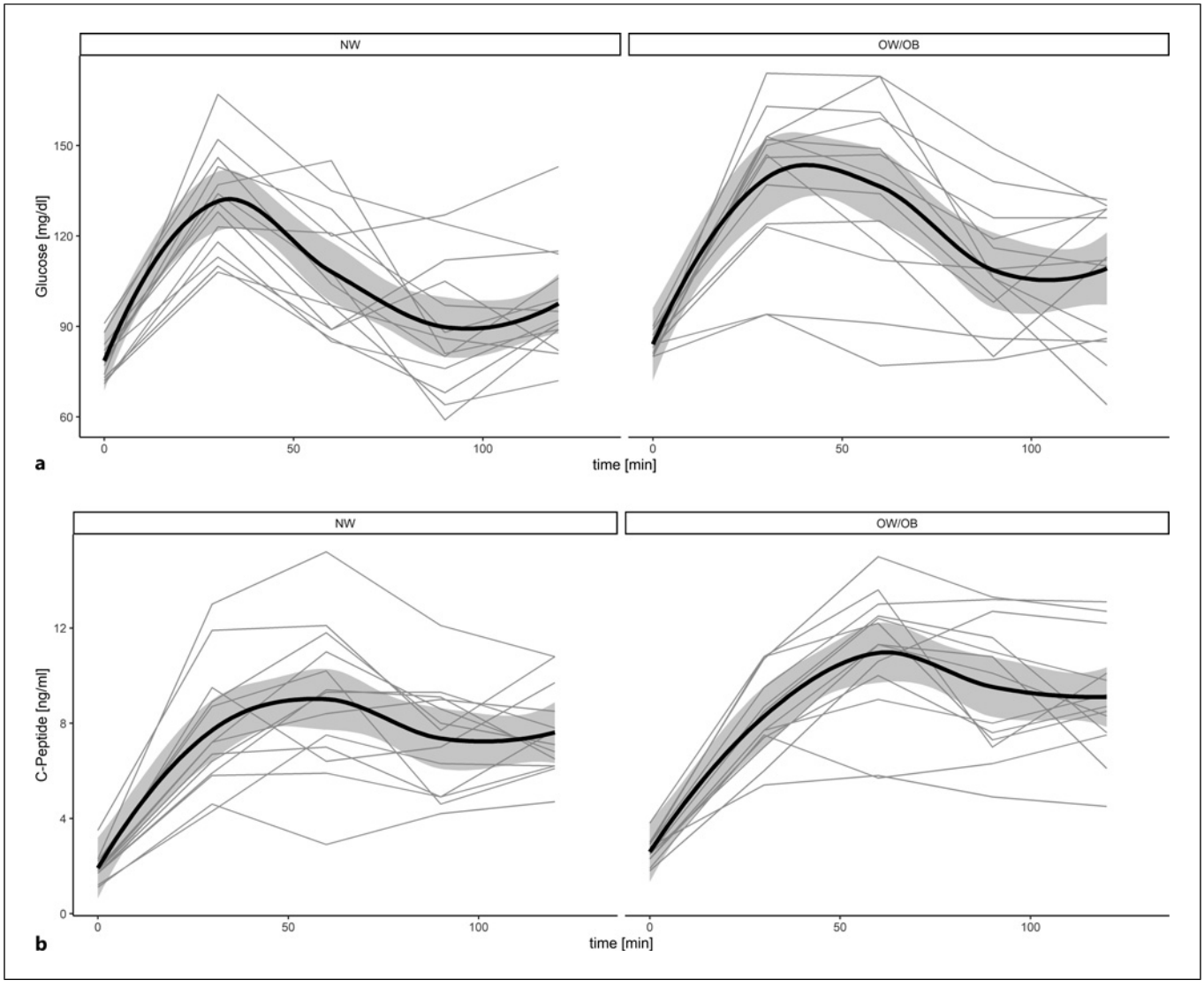

Fig. 3. Spaghetti plot of glucose and C-peptide kinetics during the OGTT in women with normal glucose tolerance at visit 2; glucose profiles (**a**); C-peptide profiles (**b**). NW, normal weight controls; OW/OB, mothers with overweight or obesity.

compared to normal weight controls [28]. In this study, we could not observe significant differences in neonatal birth weights between the two groups; however, this is probably attributable to the rather small number of subjects.

In addition to alterations in maternal glucose metabolism, obesity-associated changes in maternal lipid metabolism need to be considered as another contributor to fetal overgrowth. Several studies have shown that pregnancies complicated by obesity but not GDM result in fetal overgrowth, as well as pregnancies complicated by GDM with good glucose control [4, 29]. Higher levels of maternal triglycerides and free fatty acids might have an effect on fetal fat storage [30]. Of note, as compared to normal-weight women, mothers with overweight or obesity showed significantly elevated triglyceride levels already at the baseline examination in this study.

Pregestational obesity not only promotes the development of maternal gestational diabetes and fetal overgrowth; it has extensive consequences on the metabolic and endocrine development of the growing fetus as well. During embryonic development (the first 8 weeks after conception), environmental factors, such as changes in nutrient transport

to the embryo mediated by an unfavorable maternal endocrine environment, might lead to obesogenic fetal programming with subsequent fetal overgrowth and long-term health consequences for the offspring, such as childhood obesity or cardiovascular diseases in later life [31]. Thereby, placental nutrient transport (due to altered placental gene expression) might be either modified by an altered adipokine secretion, as suggested by some authors [32, 33], or by the chronic hyperinsulinemic environment associated with insulin resistance in mothers with obesity, as observed in this study. Noteworthy, trophoblast cells are highly sensitive to altered insulin regulation at early pregnancy, and it was shown in this context that especially the combination of maternal obesity, hyperinsulinemia, and insulin resistance has notable adverse effects on placental structure and function [34]. In line with this observation, we identified a significant association between early gestational insulin sensitivity, secretion, and placental weight, suggesting that we need to further explore the underlying pathways connecting maternal insulin resistance, placental function, and fetal overgrowth.

The data obtained by this study supports the theory of pregnancy being a stress-test for life [35], showing subtle, but clinically not yet significant metabolic changes in the early stages of pregnancy. However, as pregnancy progresses, there is an increasing physiological demand of the fetus that must be met by various adaptations of several maternal organs. Pregnancy complications, such as gestational diabetes and pregnancy-induced hypertension, might occur when one or several organs, for example the maternal pancreatic islet cells, fail to adequately adapt. Therefore, pre-existing subtle impairments in organ functionality are not only a risk factor for pregnancy complications but also for the development of various diseases in the woman's later life, as is the case with type 2 diabetes [35–38]. Pregnancy could therefore be seen as a window of opportunity, allowing to detect women at risk and to implement lifestyle changes or tighter medical care, which could positively influence the mothers' health also after pregnancy.

Advantages and limitations need to be addressed. To our knowledge, this is the first study that provides a detailed assessment of maternal glucose metabolism in early pregnancy in patients with overweight or obesity in comparison to normal weight controls. The use of an IVGTT at early pregnancy, which has been proven to be a reliable alternative to the more invasive and technically more challenging euglycemic hyperinsulinemic clamp [13], is a clear advantage of this study. The limited number of participants who gave their consent is a limitation of this study. This may be attributable to the time-consuming nature of the examination, for which only few women were willing to give consent, especially in early pregnancy. Also, recruitment took place during the COVID pandemic with very tight restrictions concerning outpatient clinic access for non-vital examinations.

In conclusion, mothers with overweight or obesity showed an unfavorable metabolic environment even at the very early stages of pregnancy, including a higher degree of insulin resistance, increased insulin secretion, and impaired beta cell functionality, as well as elevated triglycerides and CRP levels. Even patients who remained NGT during pregnancy showed significantly altered glucose and C-peptide level, and higher fasting glucose and HbA1c values during the OGTT at the beginning of the third trimester, possibly associated with lower insulin sensitivity and subtle impaired beta cell function at the start of pregnancy.

In summary, our results indicate that women affected by overweight or obesity should be considered a high-risk obstetric population requiring intensified prenatal care with special focus on glycemic control and fetal growth, even when GDM is not present. Women with overweight or obesity should be counseled with regards to lifestyle interventions (including weight gain instructions), beginning in early pregnancy or ideally when planning for pregnancy. Glucose monitoring may be considered in some cases in the presence of fetal overgrowth.

While there is room for further research to clarify the pathophysiologic processes connecting elevated maternal BMI and adverse perinatal outcomes, we conclude that pregnant patients with overweight or obesity (even those who remain NGT) should be considered high-risk patients and receive intensified medical care during pregnancy and thereafter.

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Statement of Ethics

The study was reviewed and approved by the Ethics Committee of the Medical University of Vienna, approval number 1179/2018, and performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Conflict of Interest Statement

The authors declare that they have no competing interests.

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No funding was received for this study.

Author Contributions

Christian Göbl conceived the study. Data assessment and patient recruitment were performed by Daniel Eppel, Ingo Rosicky, Grammata Kotzaeridi, Tina Linder, and Christian Göbl. Calculations and data interpretation were performed by Christian Göbl and Andrea Tura. Statistical analysis was performed by Christian Göbl. Christian Göbl prepared tables and figures. The manuscript was written by Christian Göbl and Tina Linder. Andrea Tura, Daniel Eppel, Ingo Rosicky, Grammata Kotzaeridi, Gülen-Yerlikaya-Schatten, and Micaela Morettini critically revised the manuscript. All authors reviewed and edited the final draft of the manuscript. The authors have nothing to disclose.

Data Availability Statement

The data that support the findings of this study are not publicly available due to ethical reasons but are available from the corresponding author, Christian Göbl, upon request.

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