

Article

Beta-Cell Function Assessment by In-Silico Modeling Using Three Samples from an Oral Glucose Tolerance Test During Pregnancy Possibly Complicated by Gestational Diabetes

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Abstract

Background/Objectives: In pregnancy, beta-cell function is of interest since not only insulin resistance but also beta-cell dysfunction is common, especially when gestational diabetes mellitus (GDM) occurs. Typically, model-based beta-cell function is assessed with (at least) five-sample oral glucose tolerance test (OGTT). The aim of this study was to investigate whether the clinically common three-sample OGTT is sufficient for model-based beta-cell function assessment in pregnancy. **Methods:** We studied a group of pregnant women undergoing a 2 h five-sample OGTT with glucose, insulin, and C-peptide measurement at early and/or mid-pregnancy, for a total of 152 OGTTs. The five-sample OGTT was used for model-based beta-cell function assessment, yielding three beta-cell function parameters, i.e., glucose sensitivity (GSENS), potentiation factor ratio (PFR), and rate sensitivity (RSENS). GSENS, PFR, and RSENS assessment was repeated with the three-sample OGTT (at 0, 60, 120 min) and related values were compared to those from the five-sample OGTT (reference). **Results:** We found that, for GSENS, regression and Bland–Altman analyses showed satisfactory results (conditional and marginal R^2 values: 0.56 and 0.75, $p < 0.0001$, and limits of agreement containing 94.2% of samples). Moreover, five-sample and three-sample OGTT GSENS versions were fully consistent in patient subgroup analyses. Results for PFR were less satisfactory but acceptable, whereas those for RSENS were not reliable. **Conclusions:** The three-sample OGTT is acceptable for model-based beta-cell function assessment in pregnancy, although not for all parameters. Our methodology may be used to explore the effect of time sample reduction in other in-silico models.



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1. Introduction

In-silico mathematical models have been developed over the years for the assessment of pancreatic beta-cell function in single individuals from an oral glucose tolerance test (OGTT), typically requiring 4–5 samples of glucose, insulin, and C-peptide [1–4]. During pregnancy, a 2 h OGTT is recommended for the possible diagnosis of gestational diabetes

mellitus (GDM), based on glycemia at fasting, as well as at 1 h and 2 h following the OGTT [5]. This means that in the specific condition of pregnancy, an OGTT with three samples is available in the clinical routine. This is different from other clinical conditions (such as being at risk for type 2 diabetes, T2D), where only the two-sample OGTT, with fasting and 2 h post-load glucose, is usually performed [6].

While the application of in-silico modeling for beta-cell function assessment appears unfeasible with two samples, the question arises as to whether an OGTT with three samples (as performed in pregnancy) may be sufficient for a model-based beta-cell function assessment. The interest in beta-cell function is due to the reason that beta-cell function impairment is often present in GDM (with consequences on maternal, neonatal, and perinatal outcomes) [7–20], and even postpartum in former GDM (this being relevant for later T2D) [21–33]; thus, insulin resistance (a physiological trait of pregnancy) is not the only defect observed in GDM. On the other hand, the model-based approach has proven advantageous in studying beta-cell function in women with GDM or former GDM because it is able to identify even modest beta-cell function impairment compared to simple data-driven indices (also called “empirical” indices), such as the insulinogenic index [34].

In light of the indicated superiority of the model-based approach compared to data-driven indices, and considering that a three-sample OGTT is routinely available during pregnancy, this study aims to investigate whether such an OGTT may be sufficient for a reliable model-based assessment of beta-cell function in pregnancy. For this purpose, we will compare the model-based findings obtained with three samples to those obtained with a five-sample OGTT as the reference. Specifically, we will focus on the performance of one of the mentioned beta-cell function models [4], which has already been used in previous studies in the context of pregnancy and GDM [34–36]. If we succeed in our aim, this will allow application of the model approach to several datasets, either already collected or to be collected in the future. Additionally, another aim of the study is to provide a methodological workflow to explore the effect of sample reduction in other in-silico models that are applicable to dynamic glucose test data.

2. Materials and Methods

2.1. Patients and Measures

We studied 152 OGTTs from 96 pregnant women who were recruited at the pregnancy outpatient department at the Medical University of Vienna. Women after bariatric surgery, with preconceptional (type 1 or type 2) diabetes or other endocrine disorders, HIV, hepatic infection, or malignant tumors were excluded. At early pregnancy (median gestational age of 15.9 weeks), all women underwent assessment of maternal biometry and blood tests at fasting. Women at high risk for GDM received a 2 h 75 g OGTT to assess dynamic parameters of glucose metabolism. After an overnight fast, women ingested a solution containing 75 g of glucose. Venous blood samples were taken at fasting and for 120 min (at 30, 60, 90, and 120 min) for blood glucose, insulin, and C-peptide measurements. At a median gestational age of 26.0 weeks, maternal biometry and blood tests at fasting were repeated, and a 2 h 75 g OGTT was conducted again. Thus, we collected data from 64 OGTTs at early pregnancy and 88 at mid-pregnancy (152 OGTTs in total). Of note, 56 women received both early and mid-pregnancy OGTTs. GDM was diagnosed according to international recommendations [6].

All laboratory parameters were measured according to the standard methods provided by the Clinical Institute for Laboratory Medicine (<https://labormedizin.meduniwien.ac.at/>, accessed on 9 December 2025). The data analyzed in this study were assessed within clinical investigations, described in previous studies [37,38], performed at the Medical University of

Vienna, approved by the local Ethics Committee (approval number: 1637/2014, 1179/2018), and performed in accordance with the Declaration of Helsinki (all patients provided written informed consent).

2.2. Beta-Cell Function Assessment

The in-silico model for beta-cell function assessment that we used in the present analysis was originally described in a study by Mari et al. [4], which reports details such as the expression of the model equations. In our model approach, plasma glucose and C-peptide levels measured during the OGTT are required, whereas plasma insulin level may be useful but not strictly necessary. In such a model, insulin secretion is represented as the sum of two main components, i.e., $S_g(t)$ and $S_d(t)$, where t is the time during the OGTT. The first component describes the dependence of insulin secretion on absolute plasma glucose levels (GLU), and is characterized by a nonlinear dose–response function, $f(\text{GLU})$. The mean value of the dose–response slope is named glucose sensitivity (GSENS) and represents the sensitivity to glucose of the beta cell. The dose response is modulated by a time-varying potentiation factor, $P(t)$; thus, $S_g(t) = P(t) \cdot f(\text{GLU})$. The ratio of the potentiation factor at the end of the OGTT to that at the beginning of the test is named PFR (potentiation factor ratio, which is precisely the ratio of the mean value of the potentiation factor in the 100–120 min interval to that in the 0–20 min interval). The second insulin secretion component, $S_d(t)$, describes the dynamic dependence of insulin secretion on the rate of change in glucose levels, and it is indicated as the derivative component. $S_d(t)$ is proportional to the glucose time derivative (when the glucose derivative is positive, otherwise $S_d(t)$ is null), and the proportionality constant is named rate sensitivity (RSENS). Thus, the model provides three main parameters of beta-cell function: GSENS, PFR, and RSENS. The model was first run using data from the complete (five-sample) OGTT, and hence, the derived GSENS, PFR, and RSENS parameter values were assumed as the reference values for this study. Subsequently, the model was run using data from an OGTT with restricted sampling, which included only the time samples prescribed for the GDM diagnostic OGTT, i.e., 0, 60, and 120 min (three-sample OGTT).

2.3. Data Preparation and Statistical Analysis

Data preparation and statistical analyses were performed in RStudio (version 2023.12.1 Build 402). Different statistical tests were performed to compare beta-cell function as assessed by the five-sample OGTT (the reference) and the three-sample OGTT. For more robust analysis, we first eliminated some unreliable values. For the glucose sensitivity, GSENS, it is known from previous studies that values higher than $300 \text{ pmol} \cdot \text{min}^{-1} \cdot \text{m}^{-2} \cdot \text{mM}^{-1}$ are unreliable [39]. Thus, we excluded cases where the reference GSENS (i.e., obtained with the five-sample OGTT) was higher than the indicated value. Similar criteria were applied to the potentiation factor ratio, PFR, and to the rate sensitivity (to be excluded if higher than 3 (dimensionless) and $10,000 \cdot \text{pmol} \cdot \text{m}^{-2} \cdot \text{mM}^{-1}$, respectively) [39]. Independent from the above a priori criteria, we also visually analyzed the variable value distribution for both the five-sample and the three-sample OGTT, and excluded those cases that, according to our experience, could be assumed to be outliers in relation to the specific variable distribution of the present study. We then assessed the distribution of the variables using a graphical test of normal distribution and the Shapiro–Wilk test. A square root transformation was performed in the case of skewed distribution. Following the above-described data preparation, we visually analyzed the variable distribution again and excluded cases presenting as outliers. Of note, since we performed these operations independently for each variable of interest, including the elimination of unreliable/unphysiological values or outliers, we

ended up with a slightly different number of values for the studied variables. This approach was advisable in order to include the highest number of values possible for each variable in the following analyses. Moreover, it was acceptable since each variable in this study was analyzed separately from the other variables.

After the preliminary operations described above, a comparison between the five-sample and the three-sample OGTT parameters was performed using linear regression, taking into account the repeated measures condition (some patients received both early and mid-pregnancy OGTT). This was accomplished using a linear mixed-effects model (random intercept model, using the `lme` function in the `nlme` package, available in the RStudio tool). Subsequently, we performed a Bland–Altman analysis, again considering the presence of repeated measures (with the `loa_lme` function, available in the `SimplyAgree` package).

Furthermore, to possibly get improved results, following the calculation of the variables' mean value in both the five-sample and the three-sample OGTT, we performed individual value adjustments to get the same variable mean over the five-sample and the three-sample OGTT versions. Therefore, we repeated the indicated analyses (linear regression and Bland–Altman).

We also tested the ability of each pair of variables (that is, the five-sample and the three-sample OGTT versions) to provide similar results in terms of the difference (or lack of difference) between patients divided into subgroups. Specifically, patients were divided according to glucose tolerance (GDM or non-GDM) and maternal body mass index (BMI) (overweight/obese with a maternal BMI equal to or above 27 kg/m² or non-overweight/obese with a maternal BMI less than 27 kg/m²), defined at either the early or mid-pregnancy OGTT. For this purpose, we performed the repeated measures ANOVA test.

Data are presented as mean $\pm$ standard deviation, SD. Two-tailed *p*-values less than 0.05 were considered statistically significant. All results in this study were interpreted in an exploratory manner, aiming to generate new hypotheses.

In the Supplementary Materials, Figure S1 summarizes the workflow of the described data preparation and analysis. The workflow is presented in a generic format, for possible application to other similar problems.

3. Results

3.1. Glucose Sensitivity

The focus of the results is on GSENS since it represents the main model parameters. Some basic information on PFR and RSENS are then briefly reported.

Regarding GSENS, out of the 152 OGTTs, 12 cases were excluded for the indicated a priori criterion (five-sample OGTT GSENS higher than 300 pmol·min⁻¹·m⁻²·mM⁻¹, as explained above). Afterward, following visual inspection of the distribution of variable values, two OGTTs were excluded for outlier detection in three-sample OGTT GSENS (values above 1000 pmol·min⁻¹·m⁻²·mM⁻¹). Then, since the distribution of both the five-sample and three-sample OGTT GSENS values was skewed, we used a square root transformation to achieve a normal distribution. After this transformation, we continued to perform a visual inspection of the variables' distribution and excluded one outlier in the three-sample OGTT GSENS (lower than 5 pmol·min⁻¹·m⁻²·mM⁻¹ after the square root transformation). Therefore, we ended up with 137 values to be compared between the five-sample and the three-sample OGTT GSENS. The mean value of the square root transformed five-sample OGTT GSENS was 11.30 ± 2.35 pmol·min⁻¹·m⁻²·mM⁻¹. For the three-sample OGTT GSENS, the mean value was 13.74 ± 4.12 pmol·min⁻¹·m⁻²·mM⁻¹. Of note, none of the excluded OGTTs represented GDM cases.

Linear regression analysis showed a good association between five-sample and three-sample OGTT GSENS values, with marginal and conditional R^2 values equal to 0.560 and 0.752, respectively ($p < 0.0001$). On the other hand, the three-sample OGTT GSENS tended to be higher than the five-sample OGTT GSENS. The Bland–Altman analysis emphasized the offset in the difference (i.e., bias) between the five-sample OGTT and the three-sample OGTT GSENS ($2.452 \text{ pmol} \cdot \text{min}^{-1} \cdot \text{m}^{-2} \cdot \text{mM}^{-1}$), although the limits of agreement contained 93.4% of the data (i.e., only 9 out of 137 samples were outside the limits of agreement).

Based on these findings, which indicated that the five-sample and the three-sample OGTT GSENS values are strongly related but that the three-sample OGTT GSENS overestimates the five-sample OGTT GSENS, we adjusted the former by multiplying by a factor equal to the mean of the five-sample OGTT GSENS divided by the mean of the three-sample OGTT GSENS (this factor was equal to 0.8224). This yielded the same mean value for both variables. Following this adjustment, when repeating the regression analysis, the marginal and conditional R^2 value and the p -value remained the same as those reported previously. However, the regression plot indicated that the three-sample OGTT GSENS values were more similar to those of the five-sample case (the regression plot after the adjustment is reported in Figure 1).

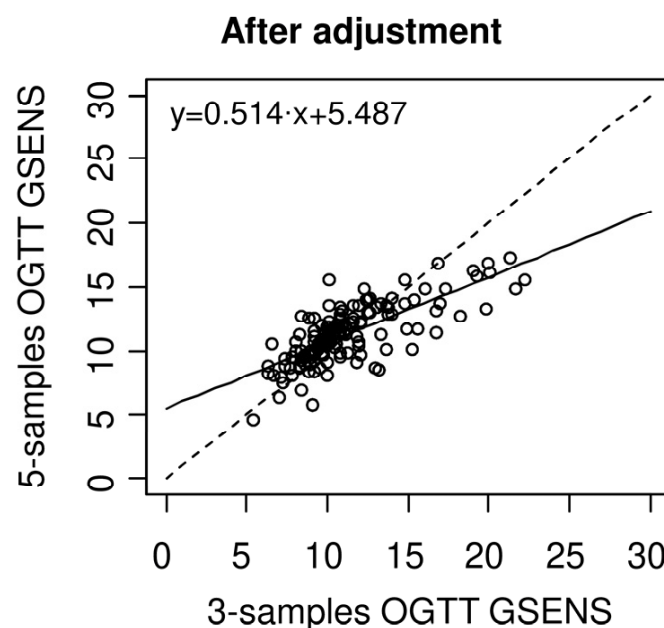


Figure 1. Linear regression plot between five-sample and three-sample OGTT square root transformed GSENS values after adjustment for the different means. Regression lines and unity lines are reported (solid and dashed lines, respectively). Marginal and conditional R^2 values are 0.560 and 0.752, respectively ($p < 0.0001$).

This result is even clearer from the Bland–Altman analysis, which shows the improvement in terms of bias (i.e., no more offset between the two variables) and has limits of agreement containing 94.2% of the data (i.e., only 8 out of 137 samples were outside the limits, as visualized in Figure 2), even though a tendency for overestimation from the three-sample OGTT GSENS remained. On the other hand, when calculating the bootstrap-based 95% CIs, we found satisfactory results, as 95% CIs were virtually the same for the five-sample and three-sample cases (10.90 – 11.69 and 10.78 – $11.91 \text{ pmol} \cdot \text{min}^{-1} \cdot \text{m}^{-2} \cdot \text{mM}^{-1}$, respectively).

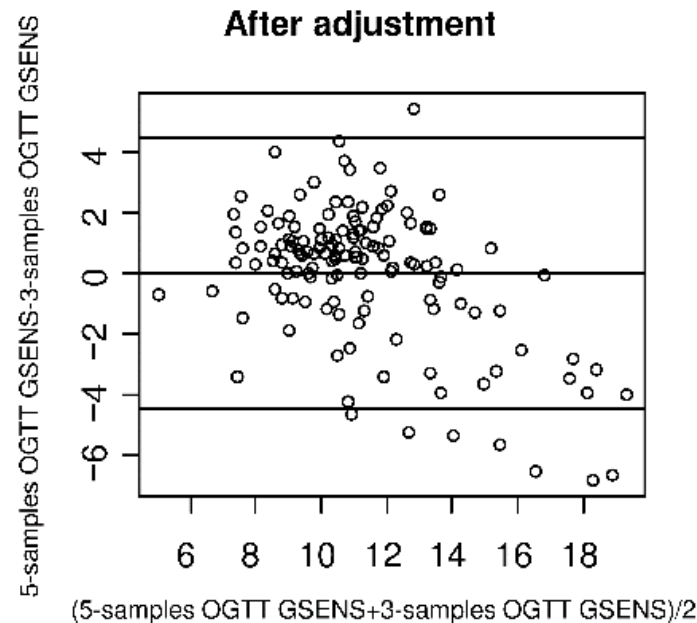


Figure 2. Bland–Altman plot for five-sample and three-sample OGTT square root transformed GSENS values after adjustment for the different means. After adjustment, offset was negligible, whereas upper and lower limits of agreement were 4.432 and $-4.458 \text{ pmol} \cdot \text{min}^{-1} \cdot \text{m}^{-2} \cdot \text{mM}^{-1}$, respectively. Solid lines are offset and limits of agreement.

Thereafter, we tested the behavior of the five-sample and the three-sample OGTT GSENS in terms of revealing differences (or lack of differences) between patient subgroups. Regarding stratification according to glucose tolerance in our cohort, we found a prevalence of GDM equal to $\sim 14.5\%$, that is, 14 cases. When testing the possible difference in GSENS between GDM and non-GDM subgroups, both the five-sample and the three-sample OGTT GSENS consistently revealed significant impairment in the former, with extremely similar p -values ($p = 0.0044$ and $p = 0.0048$, respectively). When testing possible differences between overweight/obese or non-overweight/obese subgroups ($n = 62$ and $n = 75$, respectively), no significant differences were observed, again yielding consistent results with both the five-sample and three-sample OGTT GSENS ($p = 0.49$ and $p = 0.12$, respectively).

3.2. Potentiation Factor Ratio and Rate Sensitivity

For the potentiation factor ratio, PFR, out of the 152 OGTTs, six were excluded for the indicated a priori criterion (five-sample OGTT PFR higher than 3). Following visual inspection of variable distribution, five further OGTTs were excluded as outliers in the three-sample OGTT PFR (values above 2). Then, as was done for GSENS, since both the five-sample and three-sample OGTT PFR values distribution was skewed, a square root transformation was performed. Following further visual inspection of the data, two other outliers in three-sample OGTT PFR were excluded (lower than 0.5). This resulted in 139 values to be compared between the five-sample and the three-sample OGTT PFR. Linear regression and Bland–Altman analysis showed again the need for adjustment. Therefore, we adjusted the three-sample values by again multiplying by a factor equal to the mean of the five-sample OGTT PFR divided by that of the three-sample OGTT PFR (factor equal to 1.3548). Following the adjustment, the regression plot indicated three-sample OGTT PFR values similar to those of the five-sample case (Figure 3), and the Bland–Altman analysis showed the expected improvements in terms of offset (Figure 4).

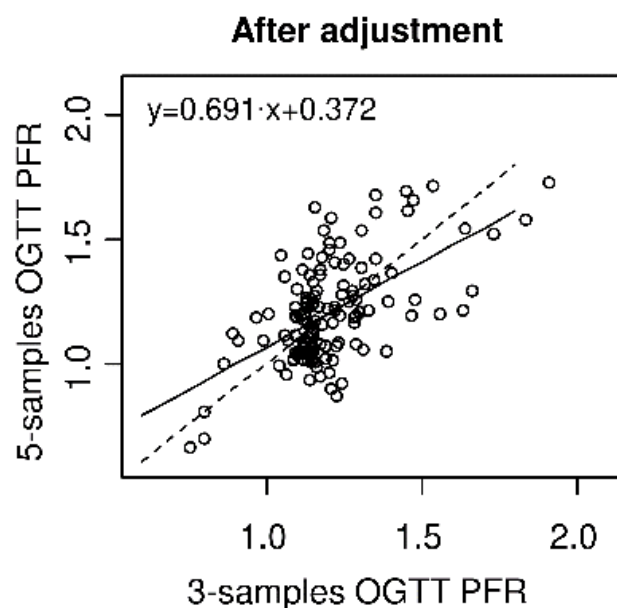


Figure 3. Linear regression plot between five-sample and three-sample OGTT square root transformed PFR values after adjustment for the different means. Regression lines and unity lines are reported (solid and dashed lines, respectively). Marginal and conditional R^2 values are 0.344 and 0.367, respectively ($p < 0.0001$).

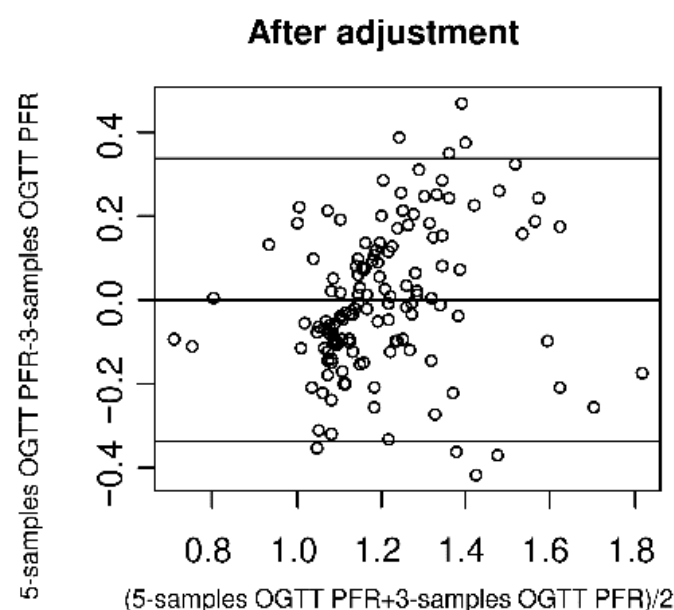


Figure 4. Bland–Altman plot for five-sample and three-sample OGTT square root transformed PFR values after adjustment for the different means. After adjustment, offset was negligible, whereas upper and lower limits of agreement were 0.339 and -0.339 , respectively. Solid lines are offset and limits of agreement.

With regard to the rate sensitivity, it is worth noting that RSENS values equal to zero (or close to zero) are possible because in some OGTTs, the early insulin secretion component is negligible. This typically happens in a relatively small number of cases; however, this was observed in several cases with the three-sample OGTT, likely due to the missing 30 min OGTT sample. Specifically, with the five-sample OGTT, RSENS was almost zero (precisely, lower than $1 \text{ pmol} \cdot \text{m}^{-2} \cdot \text{mM}^{-1}$) in 18 out of 152 cases, whereas with the three-sample OGTT, this was observed in 93 cases, leading to the conclusion that the three-sample OGTT cannot be used for reliable assessment of RSENS.

3.3. Practical Steps: How to Proceed When Analyzing a New Dataset

Based on the performed analyses and related results, in Figure 5 we summarize the workflow to be performed by investigators analyzing their own three-sample OGTT pregnancy datasets with the beta-cell function modeling approach examined in the present study. The workflow refers to the beta-cell glucose sensitivity, GSENS. However, the workflow can be similarly applied to the potentiation factor ratio, PFR, provided that the recalibration factor is 1.3548, and unreliable values are those above 3.

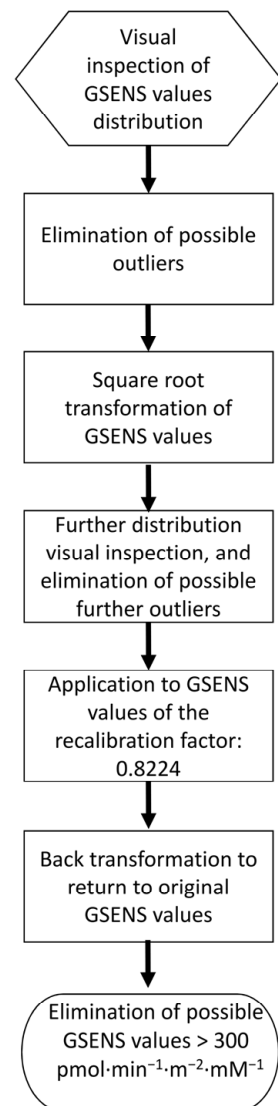


Figure 5. Workflow for the calculation of beta-cell glucose sensitivity, GSENS, from three-sample OGTT pregnancy datasets.

It is, however, worth noting that the recalibration factors may be different in different study settings. Ideally, one investigator may have his/her own initial dataset with five-sample OGTTs. In this case, the investigator may consider performing the steps reported in the present study to get his/her own (i.e., internal/center-specific) recalibration factors.

4. Discussion

In this study we have analyzed the performance of a known in-silico model for beta-cell function assessment [4] with data derived from the three-sample OGTT in pregnancy.

To our knowledge, the analyzed beta-cell function model is currently the model with a more extensive application in the field of pregnancy, as mirrored by several studies [34–36].

For the purpose of the study, the results obtained from the model [4] by the three-sample OGTT data were compared to those obtained by a five-sample OGTT, which is traditionally used for a beta-cell function modeling analysis. Of note, the methodological procedure used in this study, composed of several statistical tests applied in both the entire cohort and in derived subgroups, may be useful for future studies to assess the performance of other OGTT-based beta-cell function in-silico models. Examples of such beta-cell function models were previously mentioned [1–3]. More generically, our methodological procedure, as summarized in Figure S1, may be applied in other studies for the validation of a parameter or index derived by a new approach against the corresponding parameter/index derived by the reference method. It should also be noted that each clinical center that makes use of the model analyzed in the present study [4] should ideally calculate its own recalibration factors using an internal dataset of five-sample OGTTs.

In addition, it is worth noting that we focused on model performance with the three-sample OGTT in pregnant women, since in this category of patients, the clinical routine already recommends a three-sample OGTT to diagnose GDM [5]. However, the methodological procedure of this study may also be used in future studies on different patient populations. Indeed, the one-hour OGTT sample (i.e., glucose levels obtained at 60 min after oral ingestion) will likely become more relevant as a diagnostic parameter for type 2 diabetes. As a matter of fact, the International Diabetes Federation (IDF) is already recommending the use of a one-hour OGTT for the diagnosis of prediabetes and diabetes [40–42]. Thus, the three-sample OGTT may become clinically common not only in pregnant women, but also in several other patient categories at risk for diabetes.

It should be emphasized that in our methodological procedure we have been extremely conservative. Specifically, we excluded from the analysis OGTT cases where the modeling analyses provided results that may have been unphysiological or not reliable for computational reasons. Indeed, this introduces some lack of power in the statistical steps, but it definitely makes the whole methodology more robust, and in our experience, this aspect should be prioritized in a context such as that addressed in this study (specifically, to ensure the reliable prediction of the five-sample GSENS, i.e., the reference, through the three-sample GSENS values). Nonetheless, we explored what would happen in the eventuality that all OGTT cases were retained in the analysis. Interestingly, although the results tend to deteriorate as expected, they were still found to be relatively good, both in terms of the regression analysis and the Bland–Altman analysis, especially regarding the limited number of samples that fell out of the limits of agreement (see Supplementary Materials, Figure S2 and Figure S3, respectively). These findings further demonstrate the appropriateness and reliability of our methodological procedure.

One may wonder why the three-sample OGTT GSENS tended to overestimate the five-sample reference, whereas the PFR showed the opposite behavior. This is likely due to the reason that, in conditions where the assessment of the beta-cell function parameters may be problematic (as with three OGTT samples only), less robust parameters (PFR and RSENS, derived by the potentiation factor and by the early derivative component, respectively) tend to show a smaller effect, assuming small values. Notably, the potentiation factor and the early derivative component represent the potentiation of the “core” insulin secretion (as described by the dose–response function) and the insulin secretion increase in the early OGTT phase, respectively. Both contributions to the total insulin secretion are, however, typically modest as compared to the contribution of the dose–response. Thus, when the information provided to the model is limited (three samples only), the accurate estimation

of the potentiation factor and the early derivative component may be problematic. It is therefore possible that the estimation procedure for the model parameters converges to a “cautionary” solution, i.e., a solution that tends to minimize the size of the potentiation factor and derivative component estimates. Thus, the tendency of GSENS to assume bigger values than the “reference” values may be a compensation, and hence a consequence, of the smaller values assumed by the other parameters.

One possible source of inaccuracy in the model approach should be mentioned. Indeed, the model [4], which we have analyzed in the present study (with both five-sample and three-sample OGTT data), relies on some assumptions regarding C-peptide kinetics. Specifically, the model exploits the C-peptide kinetics calculation based on the popular method by Van Cauter et al. [43], and it remains unclear whether that method is completely suitable for pregnant women. In fact, we are not aware of studies similar to that of Van Cauter et al. [43] focusing on pregnant women. That being said, the Van Cauter method is widely used and accepted. Further, the possible effect of some related inaccuracies in the C-peptide kinetics calculation would likely be modest in our modeling approach [4], especially with regard to the model parameter of main interest, i.e., GSENS. A limitation of the study regarding the analysis of possible GSENS differences between subgroups is the small number of GDM women in the analysis. However, despite the small size of the GDM subgroup, GSENS was found, as expected, to be remarkably lower in this group. Additionally, we calculated extremely similar *p*-values between the five-sample and the three-sample OGTT GSENS analyses. This suggests that the limitation of the GDM subgroup size did not jeopardize the reliability of the subgroup analyses. Furthermore, in the analysis based on overweight/obese and non-overweight/obese subgroups, the number of women in each subgroup was well balanced, and again, we found consistency between the five-sample and the three-sample OGTT GSENS analyses.

Of note, the study of the main glucometabolic parameters in overweight/obese people that includes beta-cell function parameters may be of particular relevance since recent meta-analyses showed an increased risk of developing GDM in this category of pregnant women [44,45]. Similarly, a large meta-analysis also indicated that age is a factor clearly associated with the risk of GDM development [46]. In these contexts, the analysis of the OGTT data through in-silico beta-cell function modeling may be of particular relevance, considering the superiority of the model-based parameters in disclosing even modest beta-cell function defects that may remain undetected by the simple data-driven indices, as previously shown [34].

5. Conclusions

We have shown that in pregnancy, possibly complicated by GDM, a model-based beta-cell function assessment from OGTT with three samples only (0, 60, 120 min) is feasible, at least for the assessment of the most relevant parameter, the beta-cell glucose sensitivity. Additionally, it is worth noting that our methodology may be applied to other in-silico models for analyzing sample reduction effects.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/diabetology7030048/s1>, Figure S1: Workflow of the data preparation and analysis. The workflow is presented in generic format, for possible application to other problems where a given parameter or index calculated with a new methodology to be validated needs comparison to the same parameter or index calculated with the reference method; Figure S2: Linear regression plot between 5-samples and 3-samples OGTT square root transformed GSENS values after adjustment for the different mean, in the case of all OGTTs retained in the analysis. Regression lines and unity lines are reported (solid and dashed lines, respectively). Marginal and conditional R² are 0.470 and 0.564, respectively (*p* < 0.0001); Figure S3: Bland-Altman plot for 5-samples and 3-samples

OGTT square root transformed GSENS values after adjustment for the different mean, in the case of all OGTTs retained in the analysis. After adjustment, offset was negligible, whereas upper and lower limits of agreement were 7.375 and $-7.417 \text{ pmol} \cdot \text{min}^{-1} \cdot \text{m}^{-2} \cdot \text{mM}^{-1}$, respectively. Solid lines are offset and limits of agreement.

Author Contributions: Conceptualization, C.G. and A.T.; methodology, C.G., A.P., F.H., M.M. and A.T.; data curation, C.G. and T.L.; writing—original draft preparation, C.G. and A.T.; writing—review and editing, A.P., F.H., T.L. and M.M. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The datasets presented in this article are not readily available because the data are part of an ongoing study. Requests to access the datasets should be directed to the corresponding authors.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

BMI	Body mass index
GDM	Gestational diabetes mellitus
GSENS	Glucose sensitivity
OGTT	Oral glucose tolerance test
PFR	Potential factor ratio
RSENS	Rate sensitivity
SD	Standard deviation
T2D	Type 2 diabetes

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