

Glucose Metabolism and Modeling Approaches in Pregnancy: From Dynamic Metabolic Tests to Continuous Glucose Monitoring

Micaela Morettini¹, Agnese Piersanti¹, Andrea Tura², Christian Göbl³

¹Department of Information Engineering, Università Politecnica delle Marche, Ancona, Italy

²CNR Institute of Neuroscience, Padua, Italy

³Department of Obstetrics and Gynaecology, Medical University of Vienna, Vienna, Austria

Gestational diabetes mellitus (GDM) is increasingly recognised as a metabolically heterogeneous condition rather than a uniform disorder defined solely by diagnostic glucose thresholds. Differences in insulin resistance, insulin secretion and timing of GDM onset appear to contribute to distinct clinical patterns. Therefore, heterogeneity is likely one of GDM's central characteristics, not merely a secondary feature [1].

Regarding GDM prediction, studies in early pregnancy have shown that even simple fasting measurements can provide clinically relevant information. Fasting glucose, insulin, C-peptide, and glycosylated hemoglobin, as well as derived surrogate indices, can help to identify women at increased risk for later GDM and need for glucose-lowering therapy [2]. At the same time, dynamic testing such as the oral glucose tolerance test (OGTT) remains a reasonable alternative to fasting-only measurements because it offers more detailed insights into the underlying physiology and, specifically, into processes like insulin sensitivity and β -cell function, even not totally comparable with those offered by intravenous glucose tolerance test (IVGTT). Indeed, surrogate indices like Matsuda index (for insulin sensitivity) and insulinogenic index (for β -cell function) can be derived from OGTT data [3,4]. Despite traditionally tailored for IVGTT data, *in silico* mathematical modelling is often exploited to quantitatively capture dynamic glucose-insulin interactions, but generally it requires richer data protocols and dedicated analytic expertise. Applying models to

OGTT data makes it possible to derive detailed metabolic parameters, including insulin sensitivity, β -cell function, and insulin clearance [5]. A 'middle ground' option is designating surrogate indices that can be easily computed from shorter dynamic IVGTT tests and do not require specialized expertise, while maintaining an acceptable correlation with model-based parameters [6].

Therefore, the most relevant question is not whether fasting-only approaches are categorically better than dynamic approaches or *vice versa*, but how investigators can appropriately use each approach, depending on purposes and settings.

For instance, the traditional triglyceride-glucose index imperfectly reflect insulin sensitivity during pregnancy, whereas a pregnancy-adapted variant was specifically developed to preserve the simplicity of fasting-only assessments while improving its correlation with OGTT-derived insulin sensitivity [7]. Similarly, recent first-trimester evidence suggests that both fasting and dynamic indices can predict later GDM, though triglyceride-based fasting indices may perform particularly well in early pregnancy [8]. Taken together, these findings support a pragmatic view: dynamic indices may be physiologically richer, but thoughtfully designed fasting markers can still be highly informative for risk prediction in clinical settings [7,8].

Traditional regression-based modelling has undoubtedly advanced the field of clinical prediction models; however, metabolic data bring a familiar methodological difficulty: the rele-

Corresponding author: Christian Göbl  <https://orcid.org/0000-0002-3922-7443>
 Department of Obstetrics and Gynaecology, Medical University of Vienna, Waehringer
 Guertel 18-20, Vienna 1090, Austria
 E-mail: christian.gobl@meduniwien.ac.at

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vant variables are tightly interrelated. Glucose, insulin and C-peptide values measured at fasting or across an OGTT are not independent variables. The resulting collinearity can make interpretation less straightforward. This does not invalidate regression-based modelling, but it underscores that the complexity of metabolic data requires methods explicitly accounting for interdependence among variables [9].

This problem can be partially addressed using unsupervised learning approaches such as principal components analysis (PCA). Rather than forcing highly correlated variables into a conventional predictive framework, PCA reduces them to orthogonal components, thereby revealing dominant patterns within the metabolic data. When applied to postpartum OGTT glucose, insulin and C-peptide measurements together with age and body mass index (BMI), this approach identified three principal components explaining 71.5% of the total variance. These correspond broadly to whole-body insulin sensitivity, β -cell dysfunction and fasting or hepatic insulin resistance [10]. The value of this strategy does not lie in providing direct proof of the mechanism, but in organising complex metabolic information into dimensions that are physiologically interpretable and clinically meaningful [10].

This PCA-based framework was subsequently extended to pregnancy. The principal component scores developed from postpartum OGTT data showed patterns in pregnancy that were similar to those observed earlier in non-pregnant individuals: one component was strongly associated with peripheral insulin resistance, another with impaired insulin secretion, and a third with fasting insulin sensitivity. This supports the concept that the PCA approach can help to identify biologically relevant metabolic variation already during gestation [11].

However, what is informative in a physiological study is not necessarily easy to implement in routine care. For this reason, the transition from pathophysiological dimensions to clinically applicable phenotypes is of particular interest. The notion that GDM comprises distinct subtypes related to insulin resistance and insulin secretion has long been recognised, and more recent conceptual work has reinforced the view that subclassification may help to move the field towards greater precision [1,12]. However, routine care needs approaches that are simpler, more reproducible and easier to scale.

To this end, data-driven clustering has recently been introduced to identify meaningful risk categories. Using only maternal age, pre-pregnancy BMI and diagnostic OGTT glucose values, distinct GDM clusters were identified that differed sub-

stantially in terms of treatment requirements and in selected pregnancy outcomes. Notably, the subgroup characterised by the highest glycaemic and greatest obesity burdens had the greatest need for glucose-lowering medication and the highest risk of large-for-gestational-age infants. These findings do not imply that simple clustering fully captures the biology of GDM. Rather, they demonstrate that clinically meaningful heterogeneity can be identified even using a limited set of variables routinely available in clinical practice [13].

These concepts may be even more relevant in early pregnancy. More recent analyses indicate that the GDM subtypes identified by cluster analysis were associated with distinct glucometabolic characteristics already before the conventional diagnostic window, reinforcing the idea that the clinically important divergence between women may begin much earlier than standard screening strategies assume [14]. In parallel, first-trimester fasting and dynamic markers have also shown predictive value for later GDM, again pointing to the first half of pregnancy as a crucial period for improved metabolic stratification [8].

In addition to unsupervised data-driven approaches, supervised methods have also proven useful when model-based dynamic features are employed instead of raw data. Specifically, prior work on classifying women who do or do not progress to type 2 diabetes mellitus has highlighted the critical value of the disposition index, which requires a model-based assessment of insulin sensitivity, as the most informative feature [15].

The next step in this development is likely to come from continuous glucose monitoring (CGM). While fasting markers, dynamic testing and routine clinical clustering can only provide a partial view, CGM offers the opportunity for a more comprehensive and longitudinal description of maternal glycaemia. Prior work has already suggested that even relatively small differences in pregnancy-specific time in range may be clinically meaningful [16]. More recent interventional studies of CGM applications in pregnancies complicated with GDM have produced mixed, yet highly informative, results: some did not show benefit for their primary composite endpoint [17], whereas others reported improved outcomes despite little or no difference in the primary CGM metric [18,19].

Discrete glucose profiles have been identified by jointly considering multiple CGM metrics and circadian patterns, suggesting that prolonged hyperglycemic exposure may convey different risks than unstable glucose variability. Although this has been shown in pregestational diabetes, it illustrates an im-

portant conceptual point: clinically meaningful CGM phenotypes may only emerge when several dimensions of glucose behavior are interpreted together, rather than through a single summary metric [20].

Overall, it appears that the field has been moving from simple fasting indices to dynamic OGTT-derived surrogates, from regression methods adapted for correlated predictors to orthogonal physiological components and hence routine-data clustering, and now towards CGM-derived glucose phenotypes. The common purpose across these approaches is not methodological novelty *per se*. Rather, it is the growing recognition that GDM is metabolically heterogeneous and that this heterogeneity matters clinically. In this sense, modelling strategies have already contributed substantially to our understanding of insulin action and β -cell function in and outside of pregnancy. However, their greatest potential may lie in linking pathophysiology more closely to patient-centered and personalized care, paying particular attention to early pregnancy and the ever-expanding information content of CGM profiles.

CONFLICTS OF INTEREST

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