Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

Eur J Endocrinol. Author manuscript; available in PMC 2022 October 11.

Published in final edited form as:

Eur J Endocrinol. ; 185(5): 755–763. doi:10.1530/EJE-21-0635.

Plasma glycated CD59 predicts postpartum glucose intolerance after gestational diabetes

Katrien BENHALIMA, MD phD[1,*,#], **D Diane, MA phD**[2,#], **Annouschka LAENEN, phD**[3], **Chantal MATHIEU, MD phD**[*,1], **Jose A HALPERIN, MD**[2]

[1]Department of Endocrinology, University hospital Gasthuisberg, KU Leuven, Herestraat 49, 3000 Leuven, Belgium

[2]Divisions of Hematology, Bringham & Women's Hospital, Harvard Medical School, Boston, MA, USA

[3]Center of Biostatics and Statistical bioinformatics, KU Leuven, Kapucijnenvoer 35 bloc d – box 7001, 3000 Leuven, Belgium

Abstract

Aims: To assess whether in women with gestational diabetes mellitus (GDM), postpartum plasma glycated CD59 (pGCD59) levels predict conversion to glucose intolerance diagnosed with an oral glucose tolerance test (OGTT).

Methods: Blood levels of pGCD59 were measured in a case-control study of 105 women with GDM who underwent a 75g OGTT three months postpartum. The 35 postpartum glucose intolerant cases were individually matched for age, BMI, ethnic origin and parity with 70 women with GDM but normal postpartum OGTT (controls). The GDM cohort (105) was also matched with 105 normal glucose tolerant women during pregnancy. pGCD59 was measured by ELISA in standard peptide units (SPU).

Results: Mean pGCD59 postpartum was significantly higher in cases than in controls (1.5 ± 0.6 SPU vs. 1.0 ±0.6 SPU, p<0.001). The area under the receiving operating characteristic curve (AUC) in cases versus controls was 0.72 (95% CI 0.62–0.83) for postpartum pGCD59 and 0.50 (95% CI 0.36–0.61) for postpartum HbA_{1c}. A 0.5-unit increase in postpartum pGCD59 was associated with an OR of 3.3 (95% CI 1.82–6.16, p<0.001) for glucose intolerance postpartum. A pGCD59 cut-off postpartum of 0.9 SPU had a sensitivity of 85.7% (95% CI 69.7–95.2%),

The corresponding author: Prof Katrien Benhalima, Department of Endocrinology, UZ Gasthuisberg, Herestraat 49, 3000 Leuven, Belgium, katrien.benhalima@uzleuven.be; tel: +3216340614; fax: +3216346989.

*on behalf of the BEDIP-N investigator Group

#These authors contributed equally to this work

Author contributions

KB, CM and JH conceived the study. DM and JH performed the GCD59 analyses. KB did the literature review and wrote the first draft. All authors contributed to data interpretation and manuscript revision. The corresponding author KB had full access to all the data in the study and had final responsibility for the contents of the article and the decision to submit for publication.

Declaration of interest

JAH has a financial interest in Mellitus, LLC. Mellitus is developing diagnostic tools for diabetes. JAH's interests were reviewed and are managed by Brigham and Women's Hospital and Partners HealthCare in accordance with their conflict of interest policies. No potential conflicts of interest relevant to this article were reported.

Data availability

All data generated or analyzed during this study are included in this published article

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

specificity of 47.8% (95% CI 35.6–60.2%), positive predictive value of 45.4% (95% CI 33.1–58.2%) and negative predictive value of 86.8% (95% CI 71.9–95.6%). pGCD59 in pregnancy was a poor predictor for glucose intolerance postpartum [AUC of 0.61 (95% CI 0.50–0.72)].

Conclusions: pGCD59 might identify women at low risk for glucose intolerance postpartum and could help to avoid an OGTT.

Keywords

gestational diabetes mellitus; glucose intolerance; postpartum; biomarker

Introduction

Gestational diabetes mellitus (GDM) imparts a seven-fold increased risk of subsequent development of type 2 diabetes (T2DM) compared to women without a history of GDM (1). Women with persistent glucose intolerance [impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT)] in early postpartum are a particularly high risk group, with about 50% developing T2DM within 5 years after the delivery(2).

Professional organizations such as the American Diabetes Association (ADA), the American College of Obsterics and Gynecology, and the'International Associantion of Diabetes and Pregnancy Study Groups' recommend that women with GDM should undergo oral glucose tolerance (OGTT) testing 6–12 weeks postpartum(3–5). However, the cumbersome and time consuming nature of an OGTT makes attendance to postpartum testing in normal routine quite low, around 30–50% (6). The 'National Institute for Health and Care Excellence' (NICE) guidelines from the UK recommend therefore to not routinely offer an OGTT in early postpartum but advise instead screening after 13 weeks postpartum with a fasting plasma glucose test or HbA_{1c} if a fasting plasma glucose test is not possible(7). The low frequency of early postpartum testing in women with recent GDM highlights the need for alternative sensitive, non-fasting and easy to administer biomarkers that can be used postpartum to test women with GDM for potential conversion to glucose intolerance.

CD59 is a cell membrane-anchored complement regulatory protein that protects "self" cells from complement-mediated damage (8). Previous research has shown that human CD59 is inactivated by glycation because it contains a glycation-motiff conformed by amino acid residues K^{41}-H^{44} at the core of its active site, which centers around amino acid residue W40(9). Human studies have also shown that plasma levels of glycated CD59 (pGCD59) are significantly higher in individuals with T2DM (10). Moreover, recent studies have shown that pGCD59 is a sensitive and specific biomarker to screen for and diagnose GDM, and predict the risk of delivering a large-for-gestational age infant (11, 12). Our primary objective was to assess the accuracy of pGCD59 in predicting the results of the early postpartum OGTT conducted in women with GDM. In addition, we also aimed to determine the accuracy of HbA_{1c} compared to pGCD59 to predict glucose intolerance based on the OGTT. As a secondary aim, we assessed the association of pGCD59 levels at the time of GDM screening during pregnancy with the risk for glucose intolerance postpartum.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Patients and methods

This was a secondary analyzes of the Belgian Diabetes in Pregnancy study (BEDIP-N), which was a prospective cohort study evaluating different screening strategies for GDM (NCT02036619) (13–15). Women between 18–45 years with singleton pregnancies, and without history of diabetes or bariatric surgery, were recruited between 6–14 weeks of pregnancy. Participants without prediabetes or diabetes in early pregnancy [defined by the ADA criteria based on fasting plasma glucose level at a mean of 11 weeks], received both a non-fasting 50 g glucose challenge test (GCT) and a 75 g 2-h OGTT between 26–28 weeks of pregnancy. All participants received the OGTT irrespective of the result of the GCT. The diagnosis of GDM was based on the 2013 WHO criteria(16). A total of 2006 participants were recruited in the study. Based on the fasting glucose level in early pregnancy, 19 (0.9%) women were excluded from further screening later in pregnancy (17 women had IFG and two women had overt diabetes) and 106 (5.3%) women stopped with the study (due to medical reasons, stop at own request or loss to follow-up) before screening at 26–28 weeks(17). Of the total cohort, 1841 (91.8%) participants received an OGTT at 26–28 weeks of pregnancy, GDM prevalence was 12.5% (231)(17). The ADA recommended glycemic targets were used for the treatment of GDM [1]. If targets were not achieved with lifestyle measures, insulin therapy was added. Of all women with GDM, 14.5% (33) needed treatment with insulin during pregnancy(17).

Women with GDM were invited for an extra visit 6–16 weeks postpartum to undergo a 75 g OGTT, adjudicated based on ADA criteria to define T2DM or glucose intolerance (IFG and/or IGT). As a secondary analyzes, the diagnosis of prediabetes according to HbA_{1c} postpartum (5.7%−6.4%) using the ADA criteria was also evaluated(3). We have previously published data on the prevalence and characteristics of women with glucose intolerance in early postpartum in the BEDIP-N study(15). In short, women with GDM received a 75g OGTT at a mean of 14 ± 4.1 weeks postpartum (15). Among the 192 (83.1%) women with GDM who attended the postpartum OGTT, 35 (18.2%) had glucose intolerance [13 with IFG, 19 with IGT and 3 with IFG and IGT combined] (15, 18). Compared to women with a normal OGTT postpartum, women with glucose intolerance were more often of Asian origin, had more often a recurrent history of GDM, had higher fasting glycemia, higher HbA_{1c} and higher fasting triglycerides in early postpartum(15).

For this secondary analyzes, the 35 postpartum glucose intolerant cases were individually matched for age, BMI, ethnic origin and parity with 70 women with GDM but normal postpartum OGTT (2:1 controls to case ratio). In addition, the GDM cohort was matched for the same variables with 105 women who had normal glucose tolerance (NGT) based on the OGTT 26–28 weeks of pregnancy.

For this secondary analyzes of the BEDIP-N study, we used data and blood samples collected at the time of the postpartum OGTT and at 26–28 weeks of pregnancy. At these visits, anthropometric measurements were obtained and several self-administered questionnaires were completed (16). Weight was measured and BMI (Kg/m^2) was calculated at the diferent study visits (11 weeks, 26–28 weeks and postpartum). Ethnicity was self-reported.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

The glucose measurements of the OGTT were performed locally at each center. Glucose was analyzed immediately after the blood sample was taken. Plasma glucose was measured by an automated colorimetric-enzymatic method on a Hitachi/Roche-Modular P analyzer.

Analyzes of HbA_{1c} levels were performed centrally at the laboratory of UZ Leuven [Tosoh Automated Glycohemoglobin Analyzer HLC-723G8, coefficient of variation (CV) of 2%]. The blood samples for HbA_{1c} were stored locally at −20°C for three months before transportation to the lab of UZ Leuven.

Plasma samples used for pGCD59 and HbA_{1c} analyses were drawn simultaneously with the OGTT at 26–28 weeks gestation and with the postpartum OGTT. Plasma samples for the measurement of pGCD59 were stored at −80°C at the lab of clinical and experimental endocrinology of UZ Leuven before shipment as coded deidentified samples to the laboratory of Dr. J. Halperin (Brigham and Women's Hospital, Boston). pGCD59 was measured in standard peptide units (SPU) using the specific ELISA as described by Ghosh et al (8). Test operators were blind to the women's glucose tolerance status. The interassay CV was 3.0%. This secondary analyzes of the BEDIP-N study was approved by the Institutional Review Boards of UZ Leuven (S61532) and Partners HealthCare. We followed the Standards for Reporting of Diagnostic Accuracy guidelines for study design and reporting (19).

Statistical analyses

Comparisons of maternal characteristics between groups were performed using a two-sample t-test for continuous variables, or a Chi-square test for categorical variables. The comparison of pGCD59 levels between groups was performed using a two-sample t-test or 1-way ANOVA model; the comparison between pregnancy and postpartum pGCD59 levels was performed using a paired t-test. The discriminative power of biomarkers for postpartum glucose intolerance was analyzed by receiver operating characteristic (ROC) analysis, estimating the area under the ROC curve (AUC) with 95% confidence interval. Diagnostic accuracy measures (sensitivity, specificity, positive predictive value, negative predictive value) were estimated and presented with 95% confidence intervals. The association between pGCD59 and postpartum glucose intolerance was additionally quantified by an odds ratio (OR) for a 0,5-unit increase with 95% confidence interval, estimated from a conditional logistic regression model.

Results

Of the 231 (12.5%) women with GDM, 192 (83.1%) attended the postpartum OGTT, of which 35 (18.2%) had glucose intolerance [13 with IFG, 19 with IGT and 3 with IFG and IGT combined]. None of all women with a history of GDM, had T2DM based on the OGTT postpartum. The 35 postpartum glucose intolerant cases (with prediabetes) were individually matched with 70 women with GDM but normal postpartum OGTT (2:1 controls to case ratio). The GDM cohort was also matched with 105 NGT women in pregnancy (Figure 1).

The general maternal characteristics were similar between the GDM group in pregnancy and matched NGT group, except for significantly higher rates of a previous history of GDM in

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

the GDM group (Table 1). pGCD59 in pregnancy was 1.2 ±0.5 SPU in women with GDM compared to 0.9±0.5 SPU in NGT controls (p<0.001). Mean GCD59 in the GDM group in pregnancy was not significantly different from postpartum (1.2 ±0.5 vs. 1.2±0.6 SPU, p=0.347). At the postpartum visit, women with a history of GDM had 32.8 ± 4.8 years, BMI was 26.9 ± 5.6 kg/m², 19.2% (20) were non-Caucasian and 70.2% (73) were multiparous. pGCD59 postpartum was 1.5 ±0.6 SPU in the glucose intolerant group compared to 1.0 ±0.6 SPU in the normal postpartum group (p<0.001) (Figure 2). Mean pGCD59 values were consistently higher in glucose intolerant subjects than in the normal postpartum group across all demographic categories and in all categories of the GDM group in pregnancy (with higher pGCD59 values with increasing BMI) compared to the NGT controls in pregnancy (Table 2 and 3). Postpartum levels of pGCD59 moderately predicted glucose intolerance based on the OGTT postpartum, as shown by an AUC ROC of 0.72 (95% CI 0.62–0.83) and the accuracy was similarly high to predict IFG and IGT (Figure 3A). Of all women with GDM postpartum (105), 98.1% (103) had postpartum HbA_{1c} levels availbale, of which 11.6% (12) had prediabetes using the HbA_{1c} cut-off of 5.7%−6.4%. Only three women with glucose intolerance based on the OGTT, had also a HbA_{1c} between 5.7–6.4%, while 9 women with prediabetes according to HbA_{1c} had a normal OGTT postpartum (Figure 4). In contrast with postpartum pGCD59, postpartum HbA_{1c} had no predictive value for glucose intolerance based on the OGTT as demonstrated by an AUC ROC of 0.50 (95% CI 0.36–0.61; Figure 3B). A 0.5-unit increase in postpartum pGCD59 was associated with an OR of 3.3 (95% CI 1.82–6.15, p<0.001) for glucose intolerance. The best trade-off between sensitivity and specificity was seen at a pGCD59 cut-off postpartum of 0.9 SPU (Table 4), with a sensitivity of 85.7% (95% CI 69.7–95.2%), specificity of 47.8% (95% CI 35.6–60.2%), positive predictive value of 45.4% (95% CI 33.1–58.2%) and negative predictive value of 86.8% (95% CI 71.9–95.6%). At increasing cut-offs of pGCD59 >1.0 SPU, specificity increased but at the expense of very low sensitivity with a positive predictive value of maximum 70% and negative predictive value <80% (Table 4). Plasma gCD59 at pregnancy weeks 24–28, was a poor predictor for glucose intolerance in early postpartum with an AUC ROC of 0.61 (95% CI 0.50–0.72) (Figure 3C). In addition, HbA_{1c} at the time of the OGTT in pregnancy and the glucose values on the OGTT in pregnancy, were also poor predictors of glucose intolerance in early postpartum (Figure 3C).

Discussion

We found that postpartum pGCD59 exhibits a moderate diagnostic accuracy with high negative predictive value for glucose intolerance as diagnosed by an OGTT in early postpartum in women with GDM. In contrast, plasma glycated CD59 at the time of the OGTT in pregnancy was not a good predictor of glucose intolerance postpartum. Plasma glycated CD59 is an emerging non-fasting diabetes biomarker(10). In addition, studies have demonstrated that pGCD59 is also a sensitive and specific biomarker to screen for GDM(11, 12). We provide the first data on the diagnostic accuracy of pGCD59 to predict the OGTT in early postpartum in women with GDM. Alternative non-fasting biomarkers are needed to improve compliance with postpartum screening for glucose intolerance in women with GDM. A fasting test such as an OGTT is often considered very burdensome, especially in early postpartum when women have other priorities and often lack time. The low compliance

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

with postpartum OGTT's is a missed opportunity to timely identify and treat women with a history of GDM who are at high risk of glucose intolerance and cardiovascular disease later in life(1, 20). Women with glucose intolerance in early postpartum often have IGT, which is associated with a higher cumulative incidence of T2DM than subjects with IFG (21).

Our data show that the accuracy of pGCD59 to predict IGT was similarly high as for the prediction of IFG. We have previously shown that levels of fasting plasma glucose or HbA_{1c} alone in early postpartum fail to detect the majority of women with IGT (15). HbA_{1c} has the advantage that it is a non-fasting test which reflechts the glycemic state over a 3–4 month period. However, due to the increased red blood cell turnover in pregnancy, HbA_{1c} lacks sensitivity to screen for hyperglycemia in pregnancy(22). However, since screening with HbA_{1c} is much easier to perform than an OGTT and improves compliance with postpartum screening, the NICE guidelines do not recommend an OGTT in early postpartum but instead recommend screening with HbA_{1c} after 13 weeks postpartum as an alternative for a fasting plasma glucose test (7). We evaluated the accuracy of HbA_{1c} at a mean of 14 weeks postpartum, which should limit the impact of pregnancy on the HbA_{1c} level. Our data demonstrate that postpartum pGCD59 was a stronger predictor of glucose intolerance based on the OGTT than postpartum HbA_{1c}. Of all women with glucose intolerance based on the postpartum OGTT, only 3 women had also prediabetes based on HbA_{1c}, while 9 women with prediabetes according to HbA_{1c} had a normal postpartum OGTT. This further highlights that HbA_{1c} is a poor predictor for glucose intolerance based on the OGTT in early postpartum, while especially women with IGT based on the OGTT in early postpartum, are at high risk to develop T2DM on the long-term (21). This highlights the need for alternative accurate non-fasting biomarkers in early postpartum to improve both compliance with postpartum screening and the accuracy to timely detect glucose intolerance in this population. Our data show that a pGCD59 cut-off >1.0 SPU, had a high specificity for glucose intolerance based on the OGTT but at the expense of a very low sensitivity with a positive predictive value of max. 70% and a negative predictive value <80%. As the highest negative predictive value was seen with a pGCD59 cut-off of 0.9 SPU, we suggest that a 0.9 SPU cut-off for pGCD59 might be used to determine who has a low risk for glucose intolerance and would therefore not need an OGTT in early postpartum. In clinical practice, postpartum screening could be simplified with the measurement of pGCD59, followed by an OGTT only for those with a positive pGCD59. However, larger studies with longer follow-up are needed to further explore the most appropriate pGCD59 cut-off to determine the risk for glucose intolerance postpartum in women with a history of GDM.

Early identification of women with GDM in pregnancy at the highest risk for the development of glucose intolerance postpartum, might allow to better individualize the follow-up strategy postpartum. As the pGCD59 levels correlate with the degree of hyperglycaemia, both in pregnancy and in early postpartum, this might explain the stable pGCD59 levels from pregnancy until postpartum seen in women with GDM in our study. However, we found that pGCD59, HbA_{1c} and the glucose values at the time of the OGTT in pregnancy were poor predictors of glucose intolerance postpartum. pGCD59 at the time of the OGTT in pregnancy can therefore not be used to stratify women with GDM in pregnancy for their long-term metabolic risk.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Strengths of our study are the measurement of pGCD59 in pregnancy and postpartum. In addition, the glucose intolerant cases were matched for several important characteristics to the postpartum and pregnancy control groups. Moreover, women with prediabetes or diabetes in early pregnancy were excluded. The group with glucose intolerance postpartum does therefore not include women with pregestational diabetes. Limitations of the study are the relative small sample size and the fact that we could only evaluate conversion to glucose intolerance since none of the participants had T2DM in early postpartum. In addition, we could only evaluate the accuracy of pGCD59 in early postpartum. Since the development of glucose intolerance is increasing with longer follow-up, the accuracy of pGCD59 to predict glucose intolerance may improve over time. Larger studies with longer follow-up and longitudinal measurement of pGCD59 are needed to evaluate further its clinical utility as a biomarker to screen for glucose intolerance postpartum. An Irish propective cohort study is currently ongoing with the aim to longitudinally evaluate pGCD59 in 2000 women in pregnancy and early postpartum (23).

In conclusion, we found that postpartum measurement of pGCD59 might represent a viable alternative to identify women at low risk for glucose intolerance postpartum. Screening in early postpartum could be simplified with the measurement of pGCD59, followed by an OGTT only for those with a positive pGCD59. In contrast, plasma glycated CD59 at the time of the OGTT in pregnancy was not a good predictor of glucose intolerance postpartum.

Acknowledgements

KB is the recipient of a ‘Fundamenteel Klinisch Navorserschap FWO Vlaanderen’.

We thank all BEDIP-N centers and investigators for the collaboration in the study.

Funding

The BEDIP-N study was funded by the Belgian National Lottery, the Fund of Academic studies of UZ Leuven and the Fund Yvonne and Jacques François - de Meurs of the King Boudewijn Foundation. Work performed in the Halperin’s laboratory was funded by grants DK089206 and, DK101442 from the National Institutes of Health, USA.

The sponsors of the study had no role in the design of the study; or in the collection, handling, analysis; or interpretation of the data; or in the decision to write and submit the manuscript for publication.

References

1. Benhalima K, Lens K, Bosteels J, Chantal M. The Risk for Glucose Intolerance after Gestational Diabetes Mellitus since the Introduction of the IADPSG Criteria: A Systematic Review and Meta-Analysis. Journal of clinical medicine 2019 9 10;8(9).
2. Gerstein HC, Santaguida P, Raina P, Morrison KM, Balion C, Hunt D, Yazdi H, Booker L. Annual incidence and relative risk of diabetes in people with various categories of dysglycemia: a systematic overview and meta-analysis of prospective studies. Diabetes research and clinical practice 2007 12;78(3):305–12. [PubMed: 17601626]
3. American Diabetes A. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2020. Diabetes care 2020 1;43(Suppl 1):S14–S31. [PubMed: 31862745]
4. ACOG Practice Bulletin No. 190: Gestational Diabetes Mellitus. Obstetrics and gynecology 2018 2;131(2):e49–e64. [PubMed: 29370047]
5. International Association of D, Pregnancy Study Groups Consensus P, Metzger BE, Gabbe SG, Persson B, Buchanan TA, Catalano P, Damm P, Dyer AR, Leiva Ad, Hod M, Kitzmiler JL, et al.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes care 2010 3;33(3):676–82. [PubMed: 20190296]

6. Benhalima K, Verstraete S, Muylle F, Decochez K, Devlieger R, Crombrugge PV, Verhaegen A, Wens J, Mathieu C. Implementing a Reminder System in the Northern Part of Belgium to Stimulate Postpartum Screening for Glucose Intolerance in Women with Gestational Diabetes: The "Sweet Pregnancy" Project. International journal of endocrinology 2017;2017:3971914. [PubMed: 28775742]
7. NICE guidelines. Diabetes in pregnancy: management from preconception to the postnatal period 2015 Available from: https://www.nice.org.uk/guidance/ng3.
8. Ghosh P, Sahoo R, Vaidya A, Cantel S, Kavishwar A, Goldfine A, Herring N, Bry L, Chorev M, Halperin JA. A specific and sensitive assay for blood levels of glycated CD59: a novel biomarker for diabetes. Am J Hematol 2013 8;88(8):670–6. [PubMed: 23670858]
9. Acosta J, Hettinga J, Fluckiger R, Krumrei N, Goldfine A, Angarita L, Halperin JA. Molecular basis for a link between complement and the vascular complications of diabetes. Proc Natl Acad Sci U S A 2000;97(10):5450–5. [PubMed: 10805801]
10. Ghosh P, Vaidya A, Sahoo R, Goldfine A, Herring N, Bry L, Chorev H, Halperin JA. Glycation of the complement regulatory protein CD59 is a novel biomarker for glucose handling in humans. The Journal of clinical endocrinology and metabolism 2014 6;99(6):E999–E1006. [PubMed: 24628556]
11. Ghosh P, Luque-Fernandez MA, Vaidya A, Ma D, Sahoo R, Chorev M, Zera C, McElrath TF, Williams MA, Seely EW, et al. Plasma Glycated CD59, a Novel Biomarker for Detection of Pregnancy-Induced Glucose Intolerance. Diabetes care 2017 7;40(7):981–4. [PubMed: 28450368]
12. Ma D, Luque-Fernandez MA, Bogdanet D, Desoye G, Dunne F, Halperin JA. Plasma Glycated CD59 Predicts Early Gestational Diabetes and Large for Gestational Age Newborns. The Journal of clinical endocrinology and metabolism 2020 4 1;105(4).
13. Benhalima K, Van Crombrugge P, Moyson C, Verhaeghe J, Vandeginste S, Verlaenen H, Vercammen C, Maes T, Dufraimont E, De Block C, et al. The Sensitivity and Specificity of the Glucose Challenge Test in a Universal Two-Step Screening Strategy for Gestational Diabetes Mellitus Using the 2013 World Health Organization Criteria. Diabetes care 2018 7;41(7):e111–e2. [PubMed: 29748432]
14. Benhalima K, Van Crombrugge P, Moyson C, Verhaeghe J, Vandeginste S, Verlaenen H, Vercammen C, Maes T, Dufraimont E, De Block C, et al. Characteristics and pregnancy outcomes across gestational diabetes mellitus subtypes based on insulin resistance. Diabetologia 2019 11;62(11):2118–28. [PubMed: 31338546]
15. Benhalima K, Van Crombrugge P, Moyson C, Verhaeghe J, Vandeginste S, Verlaenen H, Vercammen C, Maes T, Dufraimont E, De Block C, et al. Prediction of Glucose Intolerance in Early Postpartum in Women with Gestational Diabetes Mellitus Based on the 2013 WHO Criteria. Journal of clinical medicine 2019 3 19;8(3).
16. Benhalima K, Van Crombrugge P, Verhaeghe J, Vandeginste S, Verlaenen H, Vercammen C, Dufraimont E, De Block C, Jacquemyn Y, Mekahli F, et al. The Belgian Diabetes in Pregnancy Study (BEDIP-N), a multi-centric prospective cohort study on screening for diabetes in pregnancy and gestational diabetes: methodology and design. BMC pregnancy and childbirth 2014;14:226. [PubMed: 25015413]
17. Benhalima K, Van Crombrugge P, Moyson C, Verhaeghe J, Vandeginste S, Verlaenen H, Vercammen C, Maes T, Dufraimont E, De Block C,et al. A Modified Two-Step Screening Strategy for Gestational Diabetes Mellitus Based on the 2013 WHO Criteria by Combining the Glucose Challenge Test and Clinical Risk Factors. Journal of clinical medicine 2018 10 13;7(10).
18. American Diabetes A Standards of medical care in diabetes−-2013. Diabetes care 2013 1;36 Suppl 1:S11–66. [PubMed: 23264422]
19. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig L, Lijmer JG, Moher D, Rennie D, de Vet HCW, et al. STARD 2015: an updated list of essential items for reporting diagnostic accuracy studies. Bmj 2015 10 28;351:h5527. [PubMed: 26511519]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

20. Kramer CK, Campbell S, Retnakaran R. Gestational diabetes and the risk of cardiovascular disease in women: a systematic review and meta-analysis. Diabetologia 2019 6;62(6):905–14. [PubMed: 30843102]

21. Richter B, Hemmingsen B, Metzendorf MI, Takwoingi Y. Development of type 2 diabetes mellitus in people with intermediate hyperglycaemia. The Cochrane database of systematic reviews 2018 10 29;10:CD012661. [PubMed: 30371961]

22. Hughes RC, Moore MP, Gullam JE, Mohamed K, Rowan J. An early pregnancy HbA1c >/=5.9% (41 mmol/mol) is optimal for detecting diabetes and identifies women at increased risk of adverse pregnancy outcomes. Diabetes care 2014 11;37(11):2953–9. [PubMed: 25190675]

23. Bogdanet D, O'Shea PM, Halperin J, Dunne F. Plasma glycated CD59 (gCD59), a novel biomarker for the diagnosis, management and follow up of women with Gestational Diabetes (GDM) - protocol for prospective cohort study. BMC pregnancy and childbirth 2020 7 18;20(1):412. [PubMed: 32682411]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

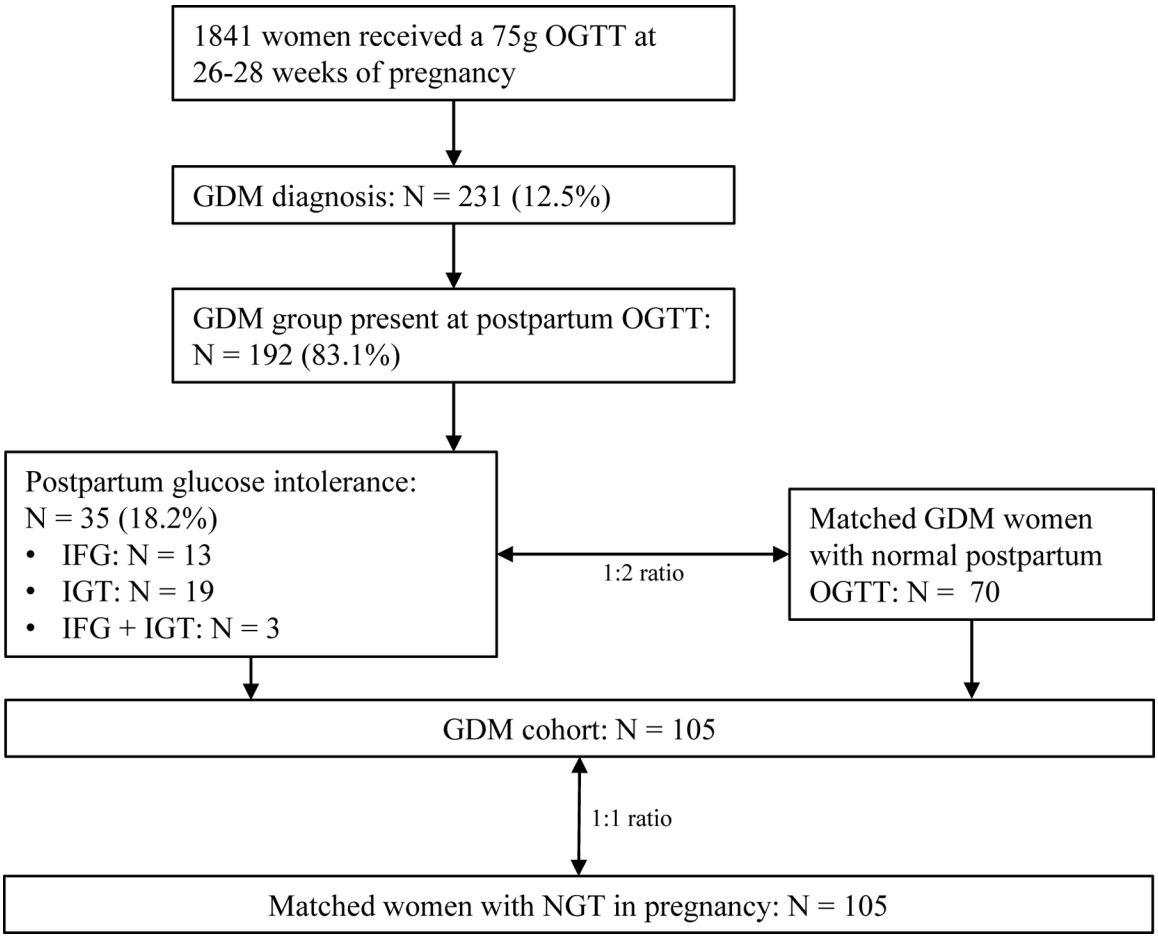


Figure 1. Flow chart of the participants

OGTT: oral glucose tolerance test; GDM: gestational diabetes mellitus; IFG: impaired fasting glucose; IGT: impaired glucose tolerance; NGT: normal glucose tolerance

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

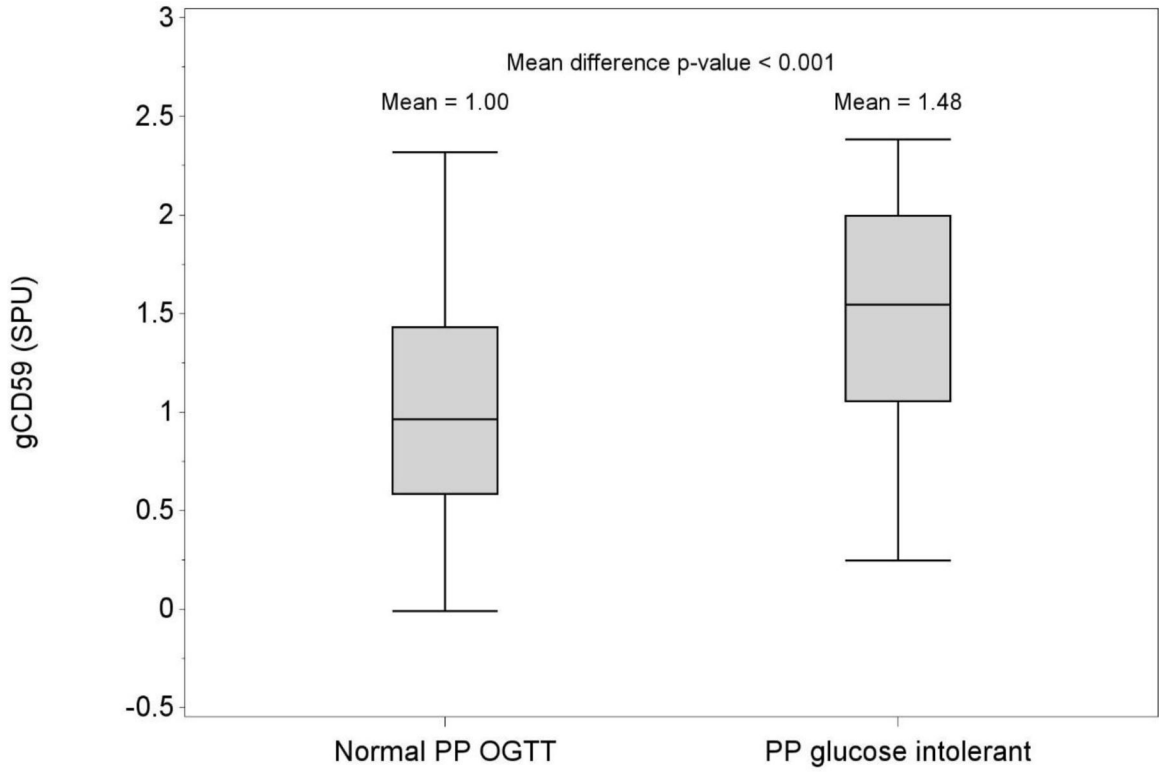
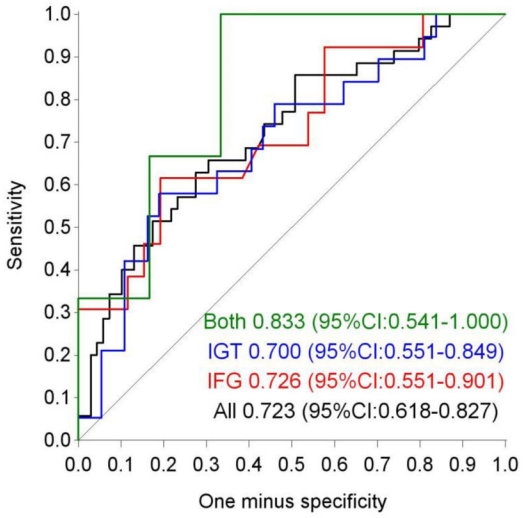


Figure 2: Distribution of postpartum pGCD59 between women with postpartum glucose intolerance and normal OGTT postpartum

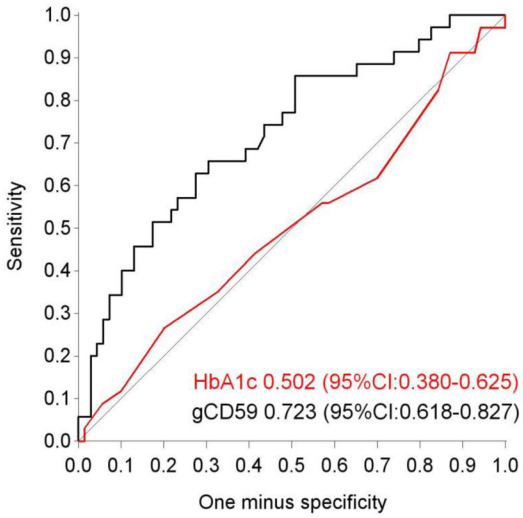
Normal PP OGTT: group with history of GDM with normal OGTT postpartum; OGTT: oral glucose tolerance test; PP glucose intolerant: group with history of GDM with glucose intolerance postpartum

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

A



B



Author Manuscript Author Manuscript Author Manuscript Author Manuscript

C

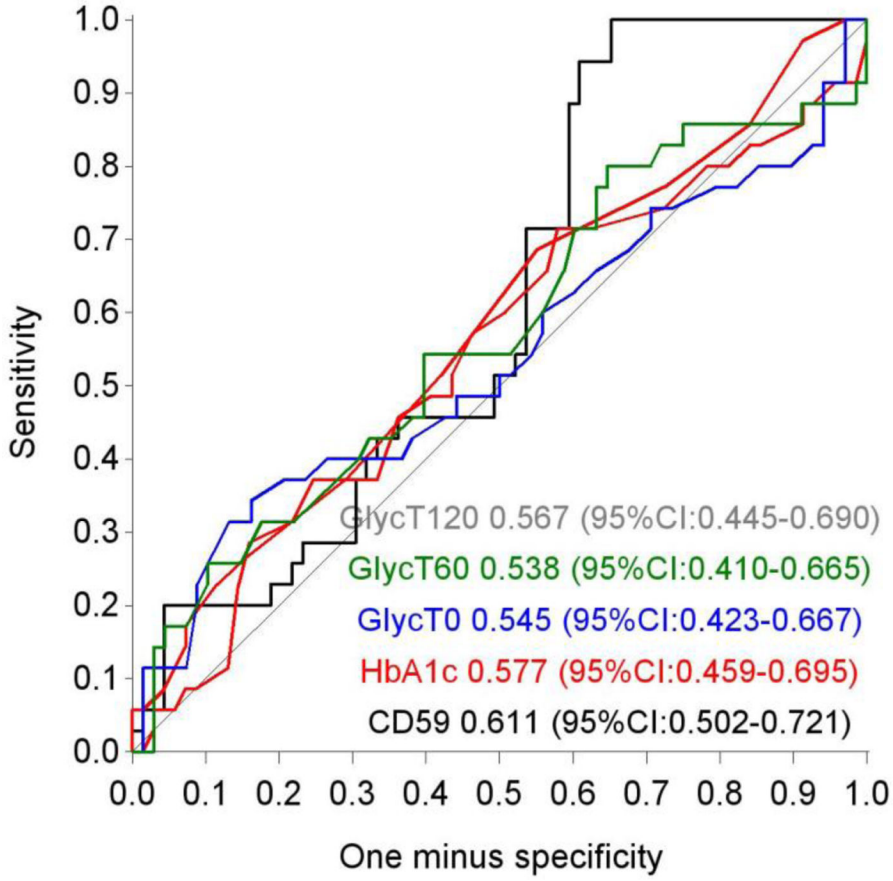


Figure 3: Receiver operating characteristic (1 ROC) curve of pGCD59 as a predictor of glucose intolerance postpartum

3A: Black line: ROC curve of pGCD59 postpartum to predict glucose intolerance [impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and both combined). Red line: ROC curve to predict isolated IFG. Blue line: ROC curve to predict isolated IGT. Green line: ROC curve to predict IFG and IGT combined.

3B: Comparison of postpartum pGCD59 (black line) and HbA1c (red line) ROC curves to predict glucose intolerance postpartum.

3C: Black line: ROC curve of pGCD59 in pregnancy to predict glucose intolerance postpartum. Red line: ROC curve of HbA1c in pregnancy to predict glucose intolerance postpartum. Blue line: ROC curve of fasting glucose level on the OGTT in pregnancy to predict glucose intolerance postpartum. Green line: ROC curve of 1 hour glucose level on the OGTT in pregnancy to predict glucose intolerance postpartum. Grey line: ROC curve of 2 hour glucose level on the OGTT in pregnancy to predict glucose intolerance postpartum. OGTT: oral glucose tolerance test

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

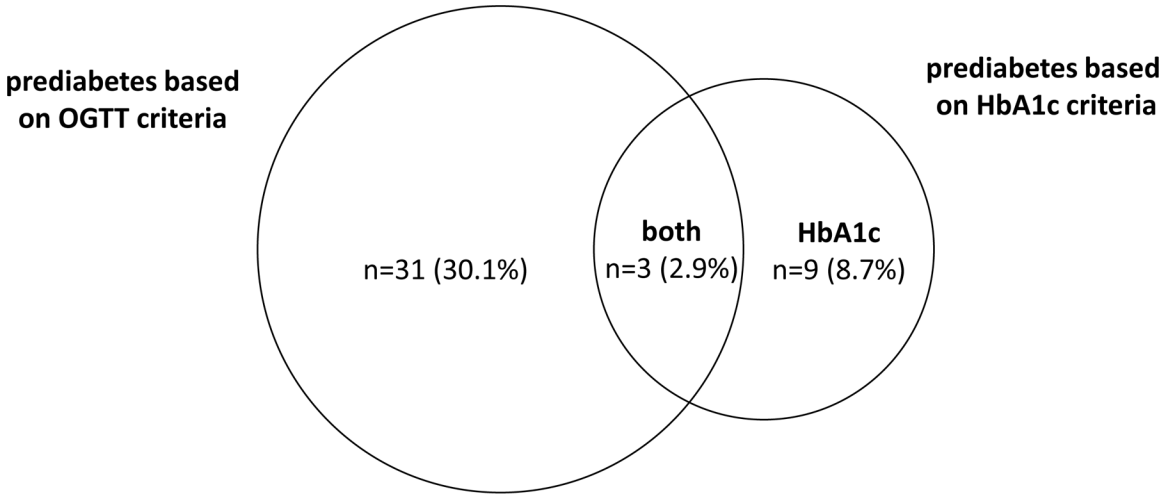


Figure 4: The number of women with a history of GDM, with glucose intolerance in early postpartum based on the OGTT and/or HbA1c postpartum

N = the number women with prediabetes based on the OGTT and/or HbA1c level (5.7–6.4%) postpartum according to the ADA criteria, % are based on the total number of women with available data on both OGTT and HbA1c postpartum (103, 98.1%).

GDM: gestational diabetes mellitus; OGTT: oral glucose tolerance test;

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 1:

Maternal characteristics of the GDM and NGT control groups in pregnancy. Data are presented as *n* (%) or as mean ± S.D.

	GDM in pregnancy	*Matched NGT control group	*P*-value
Age (years)	32.8±4.8	31.9±4.8	0.205
BMI[ǂ] (Kg/m²)	27.0±5.5	26.5±6.4	0.560
Non-Caucasian	21 (20.0)	23 (22.1)	0.708
Multiparous	74 (70.5)	71 (68.3)	0.729
Previous History of GDM	20 (27.4)	1 (1.3)	0.001
First degree family history with diabetes	23 (22.3)	13 (13.0)	0.082
Smoking during pregnancy	5 (4.8)	2 (1.9)	0.249
Education			0.855
Primary school	1 (1.0)	2 (2.0)	
Till 15 years	5 (5.0)	5 (4.9)	
High school	20 (20.0)	16 (15.8)	
Bachelor	42 (42.0)	40 (29.6)	
Master	32 (32.0)	38 (37.6)	
% Paid job	94 (90.4)	86 (81.9)	0.076
HbA1c (%(mol/mol))[†]	5.1(32)±0.3	5.0(31)±0.2	<0.001
OGTT in pregnancy			
Fasting (mg/dl)	87.5±9.3	80.1±5.8	<0.001
1 hour (mg/dl)	172.4±24.4	125.7±25.4	<0.001
2 hour (mg/dl)	154.9±27.0	112.7±21.7	<0.001

GDM: gestational diabetes mellitus; NGT: normal glucose tolerance; BMI: body mass index; OGTT: oral glucose tolerance test.

[*] the GDM cohort (105 women) was matched for age, BMI, ethnicity and parity with 105 women who had normal glucose tolerance (NGT) based on the OGTT 26–28 weeks of pregnancy;

[ǂ] At first prenatal visit;

[†] At the time of the OGTT in pregnancy

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 2

pGCD59 by maternal characteristics in the normal and glucose intolerance groups postpartum. Values are mean pGCD59 in SPU

	Glucose intolerance *n*=35		**Normal postpartum OGTT *n*=69** **	
	Values	***P*-value***	**Values**	***P*-value¥**
Age in categories (years)		0.352		0.990
<20–29	1.2±0.4		1.0±0.7	
30–34	1.4±0.7		1.0±0.6	
35–39	1.6±0.5		1.0±0.5	
≥40	2.0±0.5		0.9±0.5	
Ethnicity		0.615		0.050
Caucasian	1.5±0.6		0.9±0.6	
Non-Caucasian	1.4±0.5		1.3±0.6	
BMI at first prenatal visit (Kg/m²)		0.631		0.881
<25	1.6±0.6		1.0±0.6	
25–29.9	1.4±0.6		1.0±0.6	
≥30	1.4±0.7		1.1±0.5	
Parity		0.887		0.758
Primigravida	1.5±0.5		1.0±0.6	
Multiparity	1.5±0.6		1.0±0.6	
HbA1c postpartum (%/mmol/mol)	5.3(34) ±0.3		5.3(34) ±0.3	**0.989
OGTT postpartum (mg/dl)				
Fasting	88.7±9.1		86.0±6.7	**<0.001
2 hour	114.8±27.6		102.5±17.2	<0.001

OGTT: oral glucose tolerance test; The 35 postpartum glucose intolerant cases were individually matched for age, BMI, ethnic origin and parity with 70 women with GDM but normal postpartum OGTT (2:1 controls to case ratio). **For 1 control, pGCD59 level could not be determined.

*Overall 1-way ANOVA P value for the mean (± SD) pGCD59 differences by maternal characteristics in the glucose intolerance group

¥Overall 1-way ANOVA P value for the mean (± SD) pGCD59 differences by maternal characteristics in the normal postpartum group

**comparison of p-value between glucose intolerant and normal postpartum OGTT group

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 3:

pGCD59 by maternal characteristics in the GDM group in pregnancy and NGT control group in pregnancy. Values are presented as mean pGCD59 in SPU. The GDM cohort (105 women) was matched for age, BMI, ethnicity and parity with 105 women who had normal glucose tolerance (NGT) based on the OGTT 26-28 weeks of pregnancy.

	GDM group in pregnancy, *n*=105		**Matched NGT control group, *n*=105**	
	Values	***P*-value***	**Values**	***P*-value¥**
Age in categories (years)		0.337		0.264
<20–29	1.3±0.5		1.2±0.5	
30–34	1.3±0.5		1.1±0.5	
35–39	1.1±0.5		1.0±0.5	
≥40	1.2±0.4		1.0±0.5	
Ethnicity		0.677		0.926
Caucasian	1.2±0.5		1.1±0.5	
Non-Caucasian	1.3±0.5		1.1±0.5	
BMI at first prenatal visit (Kg/m²)		0.026		0.108
<25	1.1±0.5		1.0±0.5	
25–29.9	1.3±0.5		1.2±0.5	
≥30	1.4±0.5		1.1±0.5	
Parity		0.873		0.961
Primigravida	1.2±0.5		1.1±0.5	
Multiparity	1.2±0.5		1.1±0.5	

GDM: gestational diabetes mellitus;NGT: normal glucose tolerance

*Overall 1-way ANOVA P value for the mean (± SD) pGCD59 differences by maternal characteristics in the GDM group in pregnancy

¥Overall 1-way ANOVA P value for the mean (± SD) pGCD59 differences by maternal characteristics in the matched NGT control group

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 4:

Overview of diagnostic accuracy of pGCD59 postpartum by different cut-offs to predict glucose intolerance in early postpartum

Threshold pGCD59	Sensitivity	Specificity	Positive Predictive value	Negative predictive value
2.0				
%	22.8	94.2	66.7	70.6
95%CI	10.4–40.1	85.8–98.4	34.9–90.1	60.2–79.7
n/N	8/35	65/69	8/12	65/92
1.8				
%	34.3	92.7	70.6	73.6
95%CI	19.1–52.2	83.9–97.6	44.0–89.7	63.0–82.4
n/N	12/35	64/69	12/17	64/87
1.5				
%	51.4	82.6	60.0	77.0
95%CI	34.0–68.6	71.6–90.7	40.6–77.3	65.8–86.0
n/N	18/35	57/69	18/30	57/74
1.4				
%	57.1	72.5	51.3	76.9
95%CI	39.3–73.7	60.4–82.5	34.8–67.6	64.8–86.5
n/N	20/35	50/69	20/39	50/65
1.3				
%	62.9	69.6	51.2	78.7
95%CI	44.9–78.5	57.3–80.1	35.5–66.7	66.3–88.1
n/N	22/35	48/69	22/43	48/61
1.2				
%	65.7	62.3	49.9	78.2
95%CI	47.8–80.9	49.8–73.7	32.5–61.7	65.0–88.2
n/N	23/35	43/69	23/49	43/55
1.1				
%	74.3	56.5	46.4	81.2
95%CI	56.7–87.5	44.0–68.4	33.0–60.3	67.4–91.0
n/N	26/35	39/69	26/56	39/48
1.0				
%	77.1	50.7	44.3	81.4
95%CI	59.7–89.6	38.4–63.0	31.5–57.5	66.6–91.6
n/N	27/35	35/69	27/61	35/43
0.9				
%	85.7	47.8	45.4	86.8
95%CI	69.7–95.2	35.8–60.2	33.1–58.2	71.9–95.8

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Threshold pGCD59	Sensitivity	Specificity	Positive Predictive value	Negative predictive value
n/N	30/35	33/69	30/66	33/38
0.8				
%	85.7	36.2	40.5	83.3
95%CI	69.7–95.2	25.0–48.7	29.3–52.6	65.3–94.4
n/N	30/35	25/69	30/74	25/30

Sensitivity: n = number with pGCD59>cutoff; N = number with postpartum glucose intolerance; Specificity: n = number with pGCD59<cut-off; N = number with normal postpartum OGTT; Positive predictive value: n = number with postpartum glucose intolerance; N= number with pGCD59>cut-off; Negative predictive value: n = number with normal postpartum OGTT; N = number with pGCD59<cut-off