Development of a simple tool to predict the risk of postpartum diabetes in women with gestational diabetes mellitus

M Köhler, A G Ziegler, A Beyerlein

Institute of Diabetes Research, Helmholtz Zentrum München, and Forschergruppe Diabetes, Klinikum rechts der Isar, Technische Universität München, Ingolstädter Landstraße 1, 85764 Neuherberg, Germany (M Köhler, A G Ziegler, A Beyerlein); and Forschergruppe Diabetes e.V., Ingolstädter Landstraße 1, 85764 Neuherberg, Germany (A G Ziegler)

Corresponding author:

Prof. Dr. Anette-G. Ziegler, MD

Institute of Diabetes Research

Helmholtz Zentrum München

Ingolstädter Landstraße 1

85764 Neuherberg, Germany

Phone +49-(0)-89-3187-2896

Fax +49-(0)-89-3187-3144

E-mail: anette-g.ziegler@helmholtz-muenchen.de

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Abstract

Aim: Women with gestational diabetes mellitus (GDM) have an increased risk for diabetes postpartum. We developed a score to predict the long-term risk of postpartum diabetes using clinical and anamnestic variables recorded during or shortly after delivery.

Methods: Data from 257 GDM women who were prospectively followed for diabetes outcome over 20 years of follow-up were used to develop and validate the risk score. Participants were divided into training and test sets. The risk score was calculated using Lasso Cox regression and divided into four risk categories, and its prediction performance was assessed in the test set.

Results: Postpartum diabetes developed in 110 women. The computed training set risk score of 5 × body mass index in early pregnancy (per kg/m²) + 132 if GDM was treated with insulin (otherwise 0) + 44 if the woman had a family history of diabetes (otherwise 0) − 35 if the woman lactated (otherwise 0) had R^2 values of 0.23, 0.25, and 0.33 at 5, 10, and 15 years postpartum, respectively, and a C-Index of 0.75. Application of the risk score in the test set resulted in observed risk of postpartum diabetes at 5 years of 11% for low risk scores ≤ 140, 29% for scores 141-220, 64% for scores 221-300, and 80% for scores > 300.

Conclusion: The derived risk score is easy to calculate, allows accurate prediction of GDM-related postpartum diabetes, and may thus be a useful prediction tool for clinicians and general practitioners.

Introduction

Gestational diabetes mellitus (GDM) affects 2–6% of all pregnancies in industrialized countries [1] and is associated with an increased risk of diabetes postpartum [2,3]. We have recently reported that lactation provides long-term protection against the development of postpartum diabetes in women with GDM, while insulin treatment during pregnancy and maternal obesity are associated with increased risk [4]. These findings indicate that further stratification of GDM women according to their actual postpartum diabetes risk is possible already shortly after delivery. We aimed to develop an easily applicable tool for diabetes risk stratification in GDM women, which may be helpful in clinical settings, particularly in the context of targeted and more efficient programs to detect and prevent the development of postpartum diabetes. For this purpose, we analyzed our data with a novel approach, using advanced statistical methods to obtain a risk score based on clinical and anamnestic variables that could improve long-term prediction of postpartum diabetes in women with GDM.

Methods

Participants

The prospective German GDM study followed women with GDM from delivery for up to 20 years to detect the development of postpartum diabetes. A detailed description of the study design has been previously reported [4-6]. In brief, a total of 304 patients with GDM were recruited between 1989 and 1999 across Germany and followed up until 2014. Patients were followed for the development of diabetes postpartum by means of an OGTT at 2 and 9 months; 2, 5, 8, 11, 15, and 19 years after pregnancy; or until the diagnosis of diabetes. OGTTs were performed by the patient physician. In addition, if women presented with symptoms of diabetes between follow-up visits, physicians performed blood glucose measurements to test for clinical diabetes. Postpartum diabetes onset was defined according to American Diabetes Association criteria, which included unequivocal hyperglycemia with acute metabolic decompensation or the observation of a 2-h plasma glucose level >200 mg/dL after an oral glucose challenge, or a random blood glucose level >200 mg/dL if accompanied by unequivocal symptoms. Since 1997, a fasting blood glucose level >126 mg/dL on two occasions also was included as a diabetes diagnosis criteria in the study. Postpartum diabetes developed in 147 women (48.4%). The median postpartum follow-up time from delivery was 8.1 years for women who did not develop diabetes.

Statistical analysis

To develop the risk score we made use of the following variables: the mother's body mass index (BMI) in early pregnancy, GDM treatment (insulin or diet), family history of diabetes (yes vs. no), lactation duration (never, ≤3 months, or >3 months, coded as two dummy variables), and maternal age at delivery. These variables were collected by questionnaires or interviews and were chosen because they were easily ascertainable anamnestic information and had been previously associated with postpartum diabetes risk [4,7] .

Of the 304 women with GDM, 257 were islet autoantibody negative and had complete data for the selected variables of interest; those 257 women were used to develop and validate the risk score (suppl. table S1. Of these women, 110 developed postpartum diabetes. In order to derive and test the prediction model in two independent datasets, the data were split into a training set (2/3; n=171 women) and a test set (1/3; n=86 women) using stratified random sampling. In the training set the Lasso method for Cox regression [8] was used to reduce the final model to the most important variables to predict postpartum diabetes. We used a bootstrap approach to assess the robustness of the selection process with regards to the split into training and test set. Therefore we created 1000 different training sets of the same sample size (171 each) by sampling with replacement from the full data and assessed how often each risk factor was selected as a relevant predictor of diabetes development in those 1000 bootstrap data sets (table 1). The risk score was calculated based on the regression coefficients of the variables chosen for the final model, rounded to two decimal places and multiplied with the factor 100.

The predictive performance of the risk score in the test set was assessed with three measures: R^2 at different times after delivery to assess the overall model performance [9]; the C-Index, which is analogous to the area under the curve of logistic regression models, to assess discrimination [10]; as well as the calibration slope, which should be around 1 for a well-calibrated score, and reflects the similarity of the absolute values of the predicted risk and the observed risk over the whole time period [11].

The risk score was divided into four equally spaced intervals, and the predicted risk estimates of postpartum diabetes development in each category in the training set were compared with the respective observed diabetes rates in the test set.

All analyses were done using R version 3.0.2 [12].

Results

In the training set, insulin treatment during pregnancy, family history of diabetes, BMI in early pregnancy and lactation were selected as predictors of postpartum diabetes by the Lasso method (table 1). As the same variables

were also chosen in the majority of the 1000 bootstrap data sets, we were confident that our variable selection was robust to the split into training and test set. The risk score was derived from their regression weights as follows:

Risk score = 5 × BMI in early pregnancy (per kg/m²) + 132 if GDM was treated with insulin (otherwise +0) + 44 if the woman had a family history of diabetes (otherwise +0) − 35 if the woman lactated (otherwise -0). The risk score ranged from 54 to 380 in the training set (figure 1). The risk score showed a prediction performance in the test set with R^2 values of 0.23, 0.26, and 0.33 at 5, 10, and 15 years, a stable C-Index of 0.75, 0.75, and 0.76, respectively, and a calibration slope of 1.13.

The risk score showed values of 54 to 380 in the training set and was divided into four equally spaced risk categories corresponding to values of ≤ 140 (low), 141-220 (medium), 221-300 (high), and > 300 (very high risk). The predicted survival estimates in the training set at 5 years postpartum were 13%, 31%, 60% and 90% for the mid-interval score of the four categories. These corresponded well with the observed risks in the test set of 11%, 29%, 64%, and 80%, respectively (table 2). Additionally all observed risks in the test set fell within the confidence limits of the predicted risks (figure 2).

Conclusions

In the present study, we developed a simple risk score to predict the long-term risk of postpartum diabetes in women with GDM. The risk score may be attractive for clinicians and general practitioners because it allows them to make long-term predictions on the risk of developing postpartum diabetes based on anamnestic variables that are generally recorded during pregnancy or shortly after delivery. We identified four meaningful risk categories, which may allow the scoring system to be applied in clinical settings. All of the variables included in the final risk score calculation – insulin treatment during pregnancy, family history of diabetes, BMI in early pregnancy and lactation – have been shown to predict the risk of postpartum diabetes in earlier studies [7,13-16], supporting the plausibility of this model.

The strengths of the present article lie in the unique prospective data and long-term follow-up used to generate the models. Further, we used an established variable selection method, assessed the stability of the variable selection through bootstrap, and tested the prediction performance of the risk score in an independent test set. The latter was necessary because we were unsuccessful in our attempts to include GDM cohorts from other study groups to validate the score.

Established measures of prediction performance, including the overall model fit, discrimination, and calibration, suggested the final risk score displayed good performance, comparable to risk scores used in other medical domains [17]. For example, the algorithm developed by Hippisley-Cox and Coupland to predict the risk of venous thromboembolism based on age, BMI, smoking status, history of several cardiovascular diseases, and recent hospital admission had R^2 values of 0.33 and 0.34 in women and men, respectively, and an area under the curve of 0.75 for both sexes. Furthermore, the observed rates of postpartum diabetes in the test set were very close to the predicted risks in the training set for each risk category, indicating high validity.

Other diabetes related risk scores have been reported in the literature. Elevations in at least four out of six cardiometabolic risk factors (BMI, fasting glucose, insulin, triglycerides, high density lipoprotein cholesterol and systolic blood pressure) were found to determine a high-risk group for postpartum diabetes 10 years after delivery in 150 Australian GDM women, using a cluster analysis based approach [18]. However, data were not divided into training and test sets in this study, so that the prediction performance of the risk stratification could not be assessed, and overfitting might be an issue. In another study, a weighted genetic risk score based on 48 variants was found to slightly improve prediction of postpartum diabetes development within approximately four years after delivery in 395 Korean women with GDM history, if added to a complex model based on age, family history of diabetes, prepregnancy BMI, blood pressure, fasting glucose and fasting insulin levels [15]. Unfortunately, our data did not contain metabolic or genetic measurements, which are useful for diabetes prediction in general [19-22]. However, with a C-index of 0.75 for diabetes development after five years, the prediction performance of our risk score was almost identical to that of the Korean study, where C-indices of 0.77 and 0.74 with and without genetic markers were observed, respectively. Furthermore, measuring metabolic and particularly genetic markers requires efforts in time and money, while our risk score has the advantage of only using variables that can easily be obtained shortly after delivery. The variables in our risk score are likely to reflect underlying glycemic parameters [23], and two of them (BMI and insulin treatment) have already been suggested to be used for identification of high-risk groups suitable for targeted intervention measures [24]. Analyses of a large prospective dataset suggested that, in addition to weight and family history of diabetes, a number of further easily obtainable factors such as waist circumference, hypertension or short stature might be relevant predictors of type 2 diabetes [25]. However, these results were based on data of elderly people (aged 45-64 years) and may therefore not directly be transferable to women who recently had a GDM pregnancy, particularly as insulin treatment during pregnancy was found to be the most important predictor of diabetes development in these women.

The generalisation of our findings to populations of different (i. e. non-Caucasian) ethnic backgrounds requires verification. Furthermore, the criteria for GDM diagnosis have changed since the time when our patients were recruited, and the cohort is likely to contain also cases which would now be diagnosed as diabetes with first onset during pregnancy rather than GDM according to the current World Health Organization guidelines [1] . Due to the missing blood glucose levels at GDM diagnosis, we were not able to re-classify women according to the current WHO criteria.

In conclusion, this risk score may be an important contribution to the prediction of GDM-related postpartum diabetes, allowing practitioners to easily estimate the diabetes risk in women with prior GDM to help tailor their follow-up examinations, and clinicians to identify high-risk women for targeted prevention studies.

Contributors

MK analysed the data and wrote the first and final draft of the manuscript together with AB. AGZ designed the study, conceived the analysis, and critically revised the manuscript.

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Conflicts of Interests

The authors declare, that they have no conflicts of interest.

Statement of Human Rights

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5). The study was approved by the ethics committee of Bavaria, Germany (Bayerische Landesärztekammer Nr. 95357).

Statement of Informed Consent

All patients gave written informed consent to participate in the study.

References

1. American Diabetes Association (2011) Standards of medical care in diabetes--2011. Diabetes care 34 Suppl 1:S11–S61. doi:10.2337/dc11-S011
2. Bellamy L, Casas JP, Hingorani AD, Williams D (2009) Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. Lancet 373 (9677):1773–1779. doi:10.1016/S0140-6736(09)60731-5
3. Kim C, Newton KM, Knopp RH (2002) Gestational diabetes and the incidence of type 2 diabetes: a systematic review. Diabetes care 25 (10):1862–1868
4. Ziegler AG, Wallner M, Kaiser I, Rossbauer M, Harsunen MH, Lachmann L, Maier J, Winkler C, Hummel S (2012) Long-term protective effect of lactation on the development of type 2 diabetes in women with recent gestational diabetes mellitus. Diabetes 61 (12):3167–3171. doi:10.2337/db12-0393
5. Füchtenbusch M, Ferber K, Standl E, Ziegler A-G (1997) Prediction of type 1 diabetes postpartum in patients with gestational diabetes mellitus by combined islet cell autoantibody screening: a prospective multicenter study. Diabetes 46 (9):1459-1467
6. Löbner K, Knopff A, Baumgarten A, Mollenhauer U, Marienfeld S, Garrido-Franco M, Bonifacio E, Ziegler A-G (2006) Predictors of postpartum diabetes in women with gestational diabetes mellitus. Diabetes 55 (3):792–797
7. Henry OA, Beischer NA (1991) 11 Long-term implications of gestational diabetes for the mother. Baillière's Clinical Obstetrics and Gynaecology 5 (2):461-483. doi:10.1016/S0950-3552(05)80107-5
8. Tibshirani R (1997) The lasso method for variable selection in the Cox model. Stat Med 16 (4):385–395
9. Gerds TA, Cai T, Schumacher M (2008) The performance of risk prediction models. Biom J 50 (4):457–479. doi:10.1002/bimj.200810443
10. Gerds TA, Kattan MW, Schumacher M, Yu C (2013) Estimating a time-dependent concordance index for survival prediction models with covariate dependent censoring. Stat Med 32 (13):2173–2184. doi:10.1002/sim.5681
11. Steyerberg E (2010) Clinical Prediction Models: A Practical Approach to Development, Validation, and Updating. Springer New York,
12. Team RC (2014) R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria
13. Lee AJ, Hiscock RJ, Wein P, Walker SP, Permezel M (2007) Gestational diabetes mellitus: clinical predictors and long-term risk of developing type 2 diabetes: a retrospective cohort study using survival analysis. Diabetes care 30 (4):878–883. doi:10.2337/dc06-1816
14. Stuebe AM, Rich-Edwards JW, Willett WC, Manson JE, Michels KB (2005) Duration of lactation and incidence of type 2 diabetes. JAMA 294 (20):2601–2610. doi:10.1001/jama.294.20.2601
15. Kwak SH, Choi SH, Kim K, Jung HS, Cho YM, Lim S, Cho NH, Kim SY, Park KS, Jang HC (2013) Prediction of type 2 diabetes in women with a history of gestational diabetes using a genetic risk score. Diabetologia 56 (12):2556-2563. doi:10.1007/s00125-013-3059-x
16. Noctor E, Crowe C, Carmody LA, Kirwan B, O'Dea A, Glynn LG, McGuire BE, O'Shea PM, Dunne FP (2015) ATLANTIC-DIP: prevalence of metabolic syndrome and insulin resistance in women with previous gestational diabetes mellitus by International Association of Diabetes in Pregnancy Study Groups criteria. Acta Diabetologica 52 (1):153-160. doi:10.1007/s00592-014-0621-z
17. Hippisley-Cox J, Coupland C (2011) Development and validation of risk prediction algorithm (QThrombosis) to estimate future risk of venous thromboembolism: prospective cohort study. BMJ 343:d4656. doi:10.1136/bmj.d4656
18. Barden A, Singh R, Walters B, Phillips M, Beilin LJ (2013) A simple scoring method using cardiometabolic risk measurements in pregnancy to determine 10-year risk of type 2 diabetes in women with gestational diabetes. Nutr Diabetes 3 (6):e72. doi:10.1038/nutd.2013.15
19. Coustan DR, Carpenter MW, O'Sullivan PS, Carr SR (1993) Gestational diabetes: predictors of subsequent disordered glucose metabolism. Am J Obstet Gynecol 168 (4):1139–1144. doi:10.1016/0002-9378(93)90358-P
20. Damm P, Kühl C, Bertelsen A, Mølsted-Pedersen L (1992) Predictive factors for the development of diabetes in women with previous gestational diabetes mellitus. Am J Obstet Gynecol 167 (3):607–616. doi:10.1016/S0002-9378(11)91559-2
21. Schaefer-Graf UM, Buchanan TA, Xiang AH, Peters RK, Kjos SL (2002) Clinical predictors for a high risk for the development of diabetes mellitus in the early puerperium in women with recent gestational diabetes mellitus. Am J Obstet Gynecol 186 (4):751–756. doi:10.1067/mob.2002.121895
22. de Seymour JV, Conlon CA, Sulek K, Villas Bôas SG, McCowan LME, Kenny LC, Baker PN (2014) Early pregnancy metabolite profiling discovers a potential biomarker for the subsequent development of gestational diabetes mellitus. Acta Diabetologica 51 (5):887-890. doi:10.1007/s00592-014-0626-7

23. Ratner RE (2007) Prevention of Type 2 Diabetes in Women With Previous Gestational Diabetes. Diabetes care 30 (Supplement_2):S242-S245. doi:10.2337/dc07-s223
24. Baptiste-Roberts K, Barone BB, Gary TL, Golden SH, Wilson LM, Bass EB, Nicholson WK (2009) Risk Factors for Type 2 Diabetes Among Women with Gestational Diabetes: A Systematic Review. The American Journal of Medicine 122 (3):207-214.e204. doi:10.1016/j.amjmed.2008.09.034
25. Kahn HS, Cheng YJ, Thompson TJ, Imperatore G, Gregg EW (2009) Two risk-scoring systems for predicting incident diabetes mellitus in US adults age 45 to 64 years. Annals of Internal Medicine 150 (11):741-751

Table 1: Description and modelling results of risk factors for postpartum development of diabetes after gestational diabetes.

Variable	Median (IQR) / n (%)	HR in the Lasso model	Weight in the Lasso model[a]	Frequency (%) selected in the Lasso model[b]
BMI in early pregnancy (kg/m^2)	26.37 (23.05; 30.73)	1.05	0.05	98.0
Insulin treatment (yes)	86 (33.46%)	3.75	1.32	100
Family history of diabetes	98 (38.13%)	1.56	0.44	78.3
Lactation (yes)	204 (79.38%)	0.70	−0.35	71.3
Lactation > 3 months	28 (10.89%)			45.4
Maternal age (years)	31.40 (28.53; 34.77)			43.6

[a] The weight is the rounded log(HR) of the analysis model used in the training set.

[b] The per cent of times in which the variable was selected in 1000 bootstrap samples was determined

Abbreviations: BMI – body mass index; HR – hazard ratio, IQR - interquartile range

Table 2: Predicted risk and observed rates of diabetes at 5, 10, and 15 years postpartum by risk category according to risk score cut-off values.

Risk category	Score interval	Predicted risk (95% CI) in the training set				Observed rates (95% CI) in the test set			
		n	5 years	10 year	15 years	n	5 years	10 years	15 years
Low	< 140	83	13% (7–19%)	21% (13–29%)	26% (16–35%)	39	11% (0-21%)	15% (2-27%)	19% (4-32%)
Medium	140-220	35	31% (22–39%)	47% (36–56%)	54% (42–63%)	22	29% (6-47%)	44% (14-64%)	53% (18-74%)
High	220-300	37	60% (47–70%)	79% (66–86%)	85% (73–92%)	20	64% (30-81%)	71% (36-87%)	89% (41-98%)
Very high	> 300	16	90% (72–96%)	98% (88–100%)	99% (92–100%)	5	80% (0-97%)	–[a]	–[a]

[a]In the very-high-risk category, the survival estimate could only be determined at 5 years postpartum (80%) because 4 out of 5 women in this category had developed diabetes by 5 years after delivery, and the remaining woman was lost to follow-up after this date.

Abbreviations: CI – confidence interval

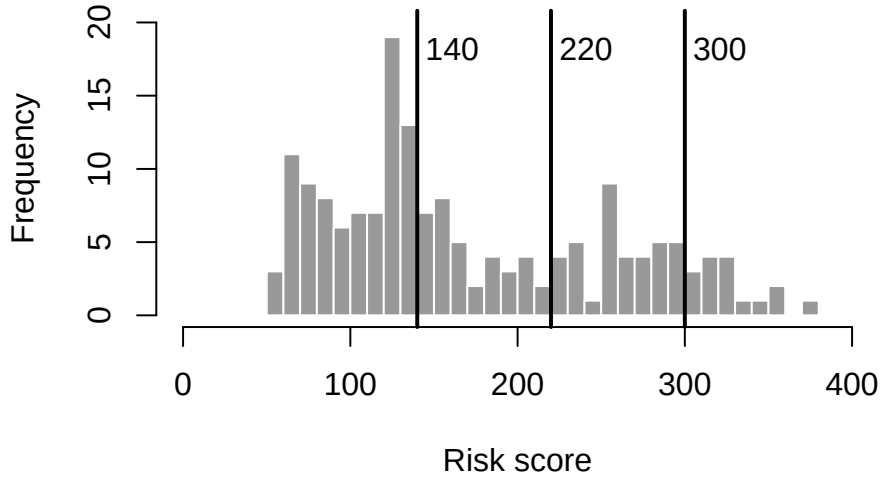

Fig 1 Histogram of the observed values of the risk score within the training set, including cutoff values for low, medium, high and very high risk

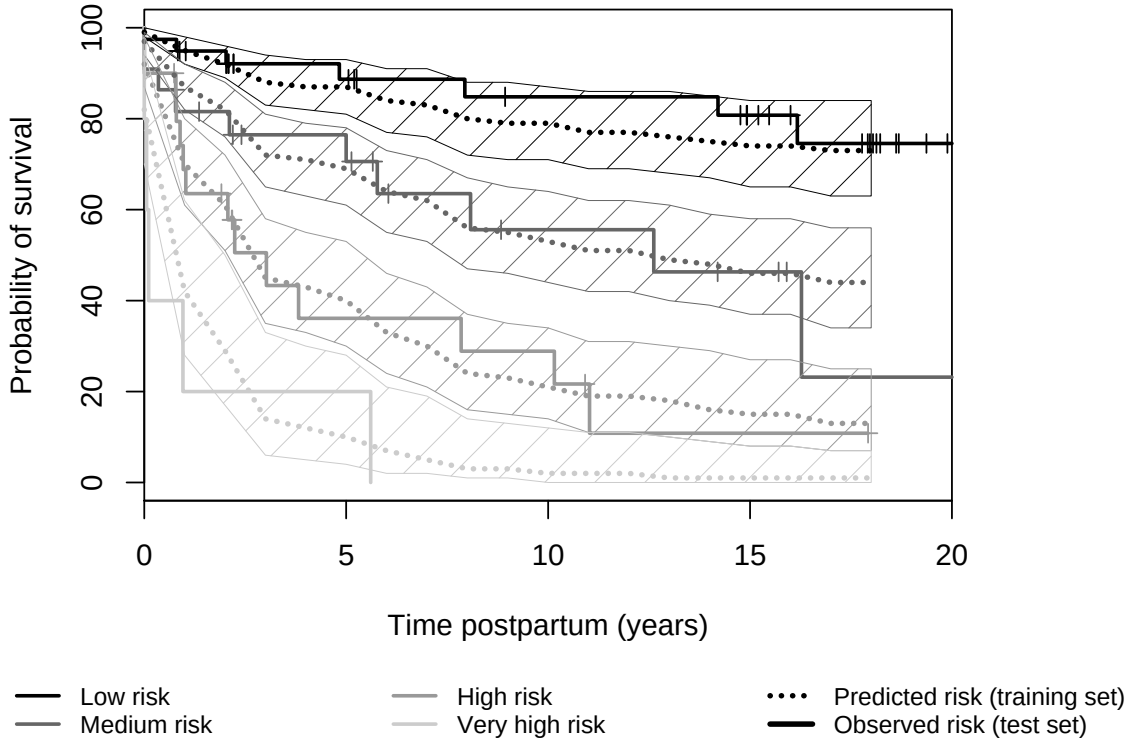

Fig 2 Predicted (training set) and observed (test set) survival curves for the four risk categories with 95% confidence intervals for each predicted survival curve

Supplementary Material

Table S1: Cohort of women with gestational diabetes [4-6].

	All	**Postpartum diabetes**
Islet autoantibody positive	28	27
Missing values on some of the variables of interest	19	10
Used for analysis	257	110
Total	304	147