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Predicting the Need for Insulin Treatment: A Risk-Based Approach to the Management of Women with Gestational Diabetes Mellitus

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Abstract: Gestational diabetes mellitus (GDM) is associated with adverse pregnancy outcomes including large for gestational age infants. Individualizing the management of women with GDM based on the likelihood of needing insulin may improve pregnancy outcomes. The aim of this study is to identify characteristics associated with a need for insulin in women with GDM, and to develop a predictive model for insulin requirement. A historical cohort study was conducted among all women with GDM in a singleton pregnancy at Aarhus University Hospital from 2012 to 2017. Variables associated with insulin treatment were identified through multivariable logistic regression. The variables were dichotomized and included in a point scoring system aiming to predict the likelihood of needing insulin. Seven variables were associated with needing insulin: family history of diabetes, current smoker, multiparity, prepregnancy body mass index, gestational age at the oral glucose tolerance test (OGTT), 2-h glucose value at the OGTT and hemoglobin A1c at diagnosis. A risk score was calculated assigning one point to each variable. On ROC analysis, a cut-off value of ≥3 points optimally predicted a requirement for insulin. This prediction model may be clinically useful to predict requirement for insulin treatment after further validation.

Keywords: gestational diabetes; pregnancy; insulin; risk score

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1. Introduction

Gestational diabetes mellitus (GDM) is defined as glucose intolerance less severe than overt diabetes with onset or first recognition during the second or third trimester of pregnancy [1].

It is well known that women with GDM are at risk of having children with high birthweight as a result of maternal hyperglycemia [2,3]. According to the Pedersen Hypothesis, maternal hyperglycemia leads to fetal hyperglycemia, resulting in fetal hyperinsulinemia and increased adipose tissue in the fetus [3]. High birthweight increases the risk of adverse pregnancy and neonatal outcomes including prolonged labor, cesarean section, shoulder dystocia, brachial plexus trauma, neonatal hypoglycemia and neonatal icterus [4]. In addition to the risks during delivery, children of women with GDM are also at high risk of developing obesity, early-onset type 2 diabetes, and metabolic syndrome [5,6], which is of great concern.

From the HAPO study, we know that the association between glycemia and adverse pregnancy outcomes including high birthweight is continuous [7], and interventional studies have found that glucose lowering treatments reduce some of these risks [8]. However, despite patients and caregivers working to obtain glycemic control through rapid and

effective treatment, the prevalence of large for gestational age infants born to women treated with insulin remains high compared to women treated with diet alone in our and in other hospitals [9,10]. One potential explanation could be that women needing insulin for optimal glycemic control commence treatment too late to impact on the risk of adverse pregnancy outcomes.

Introducing risk prediction models in the clinic could help divide women into lower and higher risk categories based on the likelihood of needing insulin. This may aid clinicians in targeting their efforts towards the women more likely to need insulin to achieve normoglycemia. As a result, the need for insulin may be identified earlier, potentially increasing treatment efficacy. Furthermore, individualizing the management of women with GDM will also be beneficial for health care systems as the prevalence of GDM continues to increase [9]. This increase in patient numbers poses a challenge with regard to the resources needed to care for this patient group.

To our knowledge, not many studies have previously tried to develop a risk prediction model for the need for insulin treatment, and they have had varying success [11–21]. Furthermore, these prediction models are probably not universally applicable, necessitating further research on predictive models for treatment in women with GDM in other composite populations.

The aims of this study were (1) to identify variables independently associated with the need for insulin and (2) to develop a pragmatic predictive model for the likelihood of needing insulin using these independent variables.

2. Materials and Methods

An observational historical cohort study was conducted at Aarhus University Hospital including all identifiable women with GDM in a singleton pregnancy from 2012 to 2017. The study population was identified using data from the Astraia software at the department (an obstetric and gynecological database containing ultrasound data) to extract a list of all women fulfilling the inclusion criteria: women with GDM in a singleton pregnancy within the specified time period giving birth to a live infant. Subsequently, the GDM diagnosis was validated during data collection from the patient records. No further exclusion criteria were applied to the study population. Data from a subset of this cohort have been published before [9].

In accordance with Danish Guidelines [22], GDM was diagnosed through selective, risk factor based screening with a 75-g oral glucose tolerance test (OGTT). GDM was defined solely on the basis of a laboratory 2-h capillary whole blood or venous plasma glucose level $\geq$ 9.0 mmol/L. Early screening at 10–20 weeks' gestation was performed in women with a previous history of GDM or at least two risk factors: prepregnancy body mass index (BMI) $\geq$ 27 kg/m^2, family history of diabetes and previous birth of a child with a birthweight $\geq$ 4.500 g (fetal macrosomia). Standard screening at 24–28 weeks' gestation was performed in women with only one risk factor or following a normal OGTT at early screening. In addition, screening was performed at any time during pregnancy when glucosuria was detected.

Following Danish guidelines [23], initial treatment for GDM consisted of dietary advice and exercise. All women had an individual dietetic consultation at the time of diagnosis outlining specific nutritional recommendations. Ambulatory glucose targets were <6.0 mmol/L before and <8.0 mmol/L one and a half hours after breakfast and dinner. Target hemoglobin A1c (HbA1c) was <5.6% (38 mmol/mol). If two or more treatment targets were exceeded within a two-week period, insulin treatment was initiated using a premixed biphasic insulin regimen (insulin aspart 30%/insulin aspart protaphane 70%; Novomix30) before breakfast and dinner. Oral hypoglycemic agents were not used.

The primary outcome was the need for insulin and the women were divided into two groups according to treatment modality i.e., GDM treated with insulin and diet (GDM-Insulin) and GDM treated with diet alone (GDM-Diet).

Data were collected on specific maternal exposure variables that could be associated with a need for insulin treatment, and therefore be potential predictor variables. The following were included: previous history of GDM, previous fetal macrosomia, family history of diabetes, smoking, ethnicity, maternal age, parity, prepregnancy BMI (based on self-reported data), gestational age at the OGTT, 2-h glucose level at the OGTT, baseline HbA1c (measured at the time of the OGTT or within the following three weeks) and HbA1c prior to delivery.

The following secondary pregnancy outcomes were included to characterize the study population: onset of labor, mode of birth, gestation at birth, infant sex, Apgar scores after delivery and birthweight. Birthweight was calculated as the standardized birthweight (Z-score) adjusted for gender and gestational age at delivery applying the method by Marsal et al. [24]. Large for gestational age was defined as Z-scores ≥ 1.3, small for gestational age as Z-scores ≤ -1.3 and the remaining infants were categorized as appropriate for gestational age. Data were obtained by extraction from computerized hospital databases, from the electronic patient records, and from the Astraia database.

Data were analyzed using StataSE version 14.1 (StataCorp Pty Ltd., College Station, TX, USA). Data distribution was examined using visual inspection of Q-Q plots. For continuous variables, mean and standard deviation were calculated for normally distributed data, and median and interquartile range were calculated for non-normally distributed data. Frequencies and percentages were calculated for categorical variables. To compare the descriptive characteristics and outcomes between treatment groups, *t*-tests were performed on all normally distributed continuous variables, Mann-Whitney U tests on all non-normally distributed continuous variables and Fisher's exact test or chi-squared tests for categorical variables.

Due to multiple exposure variables, a multivariable logistic regression model was developed to assess independent associations between potential predictor variables and insulin requirement. Potential predictor variables were included in the multivariable model on the basis of a p-value < 0.25 in the bivariable analysis. Data were analyzed excluding women with missing data on the variables being assessed. All continuous variables found to be independently associated with treatment modality were converted into dichotomized categorical variables applying the method previously reported by Barnes et al. [11]. Including all women from the original cohort, a simple, pragmatic risk score was calculated assigning one point to each of the significant variables from the multivariable logistic regression. To assess the performance of the risk prediction model, receiver operating characteristics (ROC) curve analysis was performed and the Youden Index [25] was used to determine the most appropriate risk score cut-off. Prediction statistics, along with 95% confidence intervals (CI), were then calculated for the cut-off.

The study was approved by the Danish Health Authorities (jr. 3-3013-360/1) and the Danish Data Protection Agency (jr. 1-16-02-271-13).

3. Results

3.1. Clinical Characteristics

The cohort consisted of 1104 women, with 282 (25.5%) in the GDM-Insulin group and 822 (74.5%) in the GDM-Diet group.

Maternal characteristics and pregnancy outcomes from the complete cohort have been outlined in Tables 1 and 2 stratified by treatment group. Missing data have been noted in the tables. Women with GDM-Insulin were more likely to present with a higher prepregnancy BMI (29.7 [IQR 10.3] vs. 26.1 [IQR 8.1] kg/m^2, p value < 0.001), 2-h OGTT result (10.8 [IQR 2.6] vs. 9.7 [IQR 1.1] mmol/L, p value < 0.001) and HbA1c at diagnosis (5.7 [IQR 3.0] vs. 5.3 [IQR 2.7]%, p value < 0.001) compared to women with GDM-Diet. They were also more likely to be diagnosed earlier in pregnancy equivalent to early screening (35.1 vs. 17.8%, p value < 0.001), be a smoker (14.1 vs. 3.4%, p value < 0.001) and not be nulliparous (37.2 vs. 46.8%, p value 0.005). Focusing only on multiparous women, more women with GDM-Insulin had a prior history of diabetes (50.3 vs. 29.1%, p value < 0.001)

and fetal macrosomia (9.6 vs. 6.0%, *p* value 0.117). Meanwhile, women with GDM-Diet more often had a family history of diabetes (60.0% vs. 50.4%, *p* value 0.005). There was no noticeable difference in maternal age and ethnicity, and the vast majority of women self-identified as Caucasian (87.0 and 86.6%, *p* value 0.837).

Table 1. Maternal characteristics.

Variable	Category	*n*	All GDM *n* = 1104	GDM-Diet *n* = 822	GDM-Insulin *n* = 282	*p*
Maternal age, years *		1104	31.9 (5.0)	31.8 (5.0)	32.0 (5.0)	0.513
Maternal age, years ^	≤30 >30	1104	442 (40.0%) 662 (60.0%)	328 (39.9%) 494 (60.1%)	114 (40.4%) 168 (59.6%)	0.888
Ethnicity ^	Caucasian Afro-Caribbean Asian Oriental Other		948 (86.9%) 132 (12.1%) 5 (0.5%) 4 (0.4%) 2 (0.2%)	710 (87.0%) 95 (11.6%) 5 (0.6%) 4 (0.5%) 2 (0.3%)	238 (86.6%) 37 (13.5%) 0 (0.0%) 0 (0.0%) 0 (0.0%)	0.549
Ethnicity ^	Caucasian Non-Caucasian	1091	948 (86.9%) 143 (13.1%)	710 (87.0%) 106 (13.0%)	238 (86.6%) 37 (13.5%)	0.837
Current smoker ^	Yes	1043	61 (5.9%)	27 (3.4%)	34 (14.1%)	<0.001
Prepregnancy BMI, kg/m^2 #		1100	27.1 (8.8)	26.1 (8.1)	29.7 (10.3)	<0.001
Prepregnancy BMI, kg/m^2 ^	<30 ≥30	1100	746 (67.8%) 354 (32.3%)	600 (73.3%) 219 (36.7%)	146 (52.0%) 135 (48.0%)	<0.001
Nulliparous ^	Yes	1104	490 (44.4%)	385 (46.8%)	105 (37.2%)	0.005
Prior history of GDM ^	Yes	614	216 (35.2%)	127 (29.1%)	89 (50.3%)	<0.001
Prior fetal macrosomia ^	Yes	614	43 (7.0%)	26 (6.0%)	17 (9.6%)	0.117
Family history of diabetes ^	Yes	1104	635 (57.5%)	493 (60.0%)	142 (50.4%)	0.005
Gestational age at OGTT, weeks #		1053	28 (4)	28 (4)	28 (9)	<0.001
Gestational age at OGTT, weeks ^	<24 ≥24	1053	232 (22.0%) 821 (78.0%)	141 (17.8%) 653 (82.2%)	91 (35.1%) 168 (64.9%)	<0.001
2-h OGTT result, mmol/L #		1051	9.8 (1.5)	9.7 (1.1)	10.8 (2.6)	<0.001
2-h OGTT result, mmol/L ^	<10.7 ≥10.7	1051	757 (72.0%) 294 (28.0%)	633 (79.9%) 159 (20.1%)	124 (47.9%) 135 (52.1%)	<0.001
HbA1c at diagnosis, %[mmol/mol] #		1085	5.4 (2.8) [35 (7)]	5.3 (2.7) [34 (6)]	5.7 (3.0) [39 (9)]	<0.001
HbA1c at diagnosis, %[mmol/mol] ^	<5.5 [37] ≥5.5 [37]	1085	688 (63.4%) 397 (36.6%)	595 (74.0%) 209 (26.0%)	93 (33.1%) 188 (66.9%)	<0.001
HbA1c prior to delivery, %[mmol/mol] #		915	5.5 (2.8) [37 (7)]	5.4 (2.6) [35 (5)]	5.8 (2.7) [40 (7)]	<0.001
HbA1c differences, %[mmol/mol] #		919	2.3 (2.4) [2 (3)]	2.3 (2.4) [2 (3)]	2.2 (2.7) [1 (6)]	0.032

* mean and standard deviation; # median and interquartile range; ^ frequency and percentage. GDM = Gestational diabetes mellitus. BMI = Body mass index. OGTT = Oral glucose tolerance test. HbA1c = Hemoglobin A1c. Prior history of GDM and prior history of diabetes only include multiparous women. Missing data are noted in the table.

Table 2. Labor and delivery outcomes.

Variable	Category	*n*	All GDM *n* = 1104	GDM-Diet *n* = 822	GDM-Insulin *n* = 282	*p*
Onset of labor ^	Spontaneous	1032	448 (25.2%)	377 (45.9%)	71 (25.2%)	<0.001
	Induction of labor		447 (50.4%)	305 (37.1%)	142 (50.4%)	
	C-section		137 (12.4%)	76 (9.3%)	61 (21.6%)	
Mode of birth ^	Vaginal	1098	771 (70.2%)	604 (73.7%)	167 (60.1%)	<0.001
	Vacuum		26 (2.4%)	15 (1.8%)	11 (4.0%)	
	Elective C-section		153 (13.9%)	98 (12.0%)	55 (19.8%)	
	Emergency C-section		148 (13.5%)	103 (12.6%)	45 (16.2%)	
Gestation at birth, weeks #		1104	39 (2)	39 (2)	38 (1)	<0.001
Infant sex ^	Female	1104	512 (46.4%)	378 (46.0%)	134 (47.5%)	0.678
	Male		592 (53.6%)	444 (54.0%)	148 (52.5%)	
Apgar 1 min #		1072	10 (1)	10 (1)	10 (1)	0.002
Apgar 5 min #		1069	10 (0)	10 (0)	10 (0)	0.007
Apgar 10 min #		997	10 (0)	10 (0)	10 (0)	0.419
Birthweight, grams *		1103	3515 (556)	3464 (530)	3663 (603)	<0.001
Birthweight, Z-score *		1103	0.24 (1.24)	0.032 (1.10)	0.87 (1.44)	<0.001
Size category ^	SGA	1103	94 (8.5%)	76 (9.3%)	18 (6.4%)	<0.001
	AGA		813 (73.7%)	652 (79.3%)	161 (57.3%)	
	LGA		196 (17.8%)	94 (11.4%)	102 (36.3%)	

* mean and standard deviation; # median and interquartile range; ^ frequency and percentage. GDM = Gestational diabetes mellitus. SGA = Small for gestational age. AGA = Appropriate for gestational age. LGA = Large for gestational age. Missing data are noted in the table.

As reported earlier (9), women with GDM-Insulin had infants with a higher mean birthweight (3663 [SD 603] vs. 3464 [SD 530] grams, p value < 0.001), and they were more likely to deliver a large for gestational age infant (36.3 vs. 11.4%, p value < 0.001) compared to women with GDM-Diet. Furthermore, the most common onset of labor in the GDM-Insulin treatment group were induction of labor compared to spontaneous labor in the GDM-Diet treatment group. The frequency of caesarean section, elective or emergency, were also highest in the GDM-Insulin treatment group.

3.2. Multivariable Logistic Regression

The results of the bivariable and multivariable logistic regression, examining variables associated with a requirement for insulin treatment, have been shown in Table 3. Due to missing data in the independent variables the sample size for the multivariable regression was 978 women. Prior history of GDM and prior history of fetal macrosomia were excluded from the analysis, because they were not relevant for nulliparous women and consequently reduced sample size significantly. Furthermore, HbA1c at diagnosis was the only HbA1c value included due to collinearity.

The multivariable logistic regression identified five variables that were independently associated with the need for insulin (Table 3). Parity and family history of diabetes were associated with insulin treatment on the bivariable analysis, but after adjustment the significance level shifted. However, they were retained in the model due to their clinical relevance and routine ascertainment. A risk score for the need for insulin treatment during pregnancy were calculated assigning one point to each factor and including all women from the original cohort. The highest number of positive factors present in any individual participant was six. Hence the final risk score ranged between zero and six points.

Table 3. Results of bivariable and multivariable logistic regression (outcome: treatment).

			Bivariable ***n*** **= 1104**			**Multivariable** ***n*** **= 978**	
Variable	**Category**	**OR**	**95% CI**	***p***	**aOR**	**95% CI**	***p***
Family history of diabetes	No	0.68	0.52, 0.89	0.005	0.87	0.61, 1.24	0.426
	Yes	1	—	—	1	—	—
Current smoker	Smoker	4.69	2.76, 7.94	<0.001	4.20	2.21, 8.01	<0.001
	Non-smoker	1	—	—	1	—	—
Parity	Nulliparous	1	—	—	1	—	—
	Multiparous	1.49	1.13, 1.96	0.005	1.39	0.96, 2.00	0.078
Prepregnancy BMI, kg/m^2	<30	1	—	—	1	—	—
	≥30	2.53	1.91, 3.35	<0.001	1.71	1.19, 2.46	0.004
Gestational age at OGTT, weeks	<24	2.51	1.83, 3.43	<0.001	2.86	1.92, 4.26	<0.001
	≥24	1	—	—	1	—	—
2-h OGTT result, mmol/L	<10.7	1	—	—	1	—	—
	≥10.7	4.33	3.21, 5.85	<0.001	3.16	2.19, 4.57	<0.001
HbA1c at diagnosis, %[mmol/mol]	<5.5 [37]	1	—	—	1	—	—
	≥5.5 [37]	5.76	4.29, 7.72	<0.001	3.79	2.64, 5.44	<0.001

BMI = Body mass index. OGTT = Oral glucose tolerance test. HbA1c = Hemoglobin A1c. OR = Odds ratio. CI = Confidence interval. aOR = adjusted odds ratio.

Finally, the fit of the developed prediction model was evaluated on the study population. The women were distributed based on number of risk factors present. The median (IQR) risk score was 3 (2–4) for women with insulin treatment and 2 (1–3) for those with diet treatment (p value < 0.001; Mann-Whitney U test) (Figure 1). Using the Youden index, the optimal cut-off for the prediction of treatment was a risk score of ≥3 points. The cross-tabulation with treatment has been displayed in Table 4. A receiver operating characteristics curve analysis using the risk score to predict treatment found an area under the curve for treatment at 0.754 (95% CI 0.72–0.79) (Figure 2).

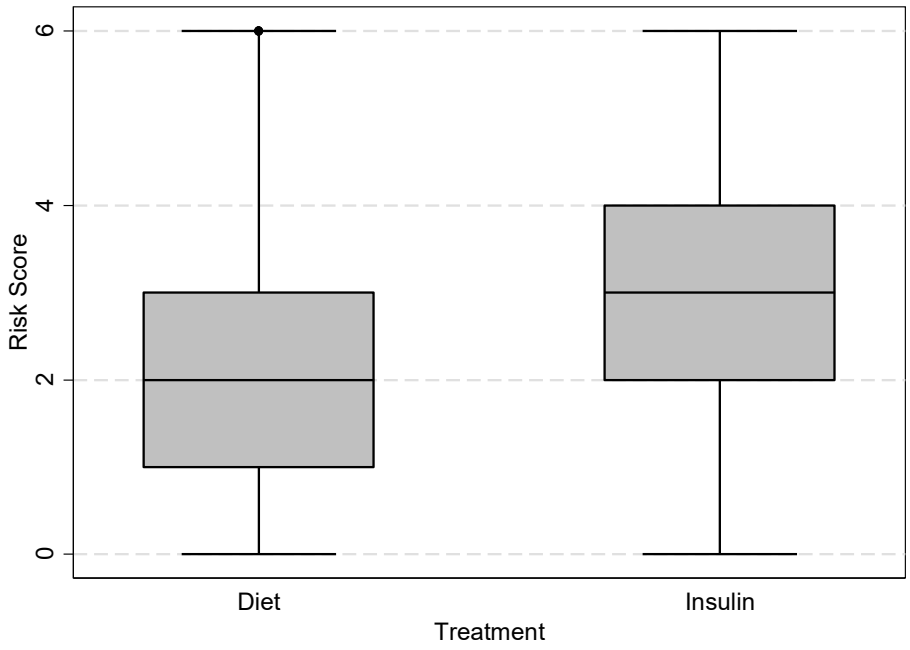

Figure 1. Boxplot of risk score vs. treatment type.

Table 4. Risk score tabulation and prediction statistics for treatment (outcome: treatment).

Risk Score Tabulation				Prediction Statistics for Treatment			
Risk Score	**Total** ***n*** **= 1104**	**GDM-Diet** ***n*** **= 822**	**GDM-Insulin** ***n*** **= 282**	**Risk Score**	**Total** ***n*** **= 1104**	**GDM-Diet** ***n*** **= 822**	**GDM-Insulin** ***n*** **= 282**
0	37 (3.4%)	36 (4.4%)	1 (0.4%)	<3	642 (58.2%)	565 (68.7%)	77 (27.3%)
1	275 (24.9%)	250 (30.4%)	25 (8.9%)	≥3	462 (41.9%)	257 (31.3%)	205 (72.7%)
2	330 (29.9%)	279 (33.9%)	51 (18.1%)	Total	1104 (100.0%)	822 (100.0%)	282 (100.0%)
3	263 (23.8%)	175 (21.3%)	88 (31.2%)	Sensitivity 72.7% (95% CI 67.1, 77.8)			
4	144 (13.0%)	62 (7.5%)	82 (29.1%)	Specificity 68.7% (95% CI 65.4, 71.9)			
5	43 (3.9%)	16 (2.0%)	27 (9.6%)	PPV 44.4% (95% CI 39.8, 49.0)			
6	12 (1.1%)	4 (0.5%)	8 (2.8%)	NPV 88.0% (95% CI 85.2, 90.4)			

Accuracy 69.7%. Odds ratio 5.85 (95% CI 4.34, 7.90). CI = Confidence interval. PPV = Positive predictive value. NPV = Negative predictive value. OR = Odds ratio.

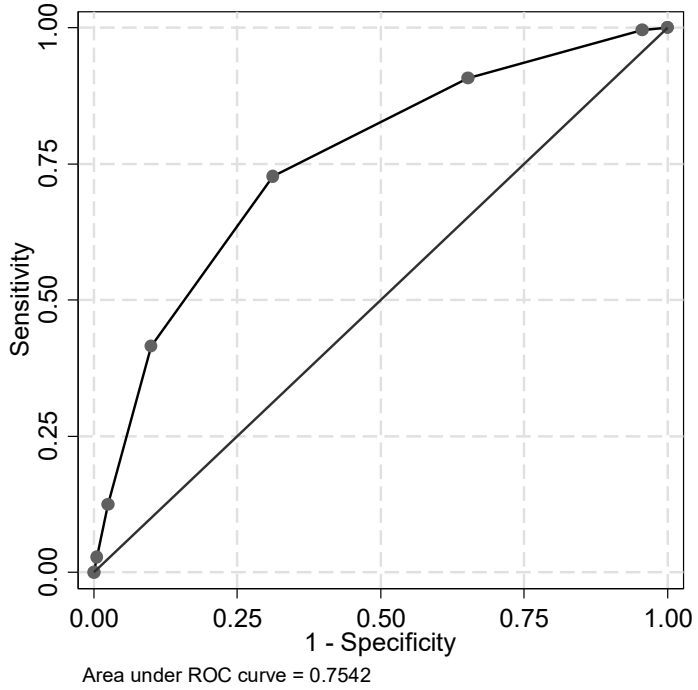

Figure 2. Receiver operating characteristics curve (ROC) for treatment and risk score. The area under the curve (AUC) for treatment was 0.7542 (95% confidence interval 0.722, 0.786).

3.3. Prediction Statistics for Treatment

Setting a cut-off value of ≥3 points for the need of insulin, the odds ratio (OR) (95% CIs) for needing insulin compared to diet treatment only was 5.85 (4.34–7.90) with a specificity of 68.7% (65.4–71.9%), a sensitivity of 72.7% (67.1–77.8%), a negative predictive value (NPV) of 88.0% (85.2–90.4%) and a positive predictive value (PPV) of 44.4% (39.8–49.0%) (Table 4).

4. Discussion

In women with GDM, we identified seven variables associated with a need for insulin, and we used these variables to create a simple, pragmatic prediction model for a requirement for insulin treatment. We suggest that such a model may assist in stratifying women with GDM into lower and higher risk categories based on their likelihood of needing insulin, allowing triage into different levels of care in the clinic.

In our study population, 642 women (58.2%) had a risk score below three substantially decreasing the likely need for insulin treatment (NPV of 88.0%). They could be categorized as low risk and therefore allocated to a less intensive surveillance program. The remaining 462 women (41.8%) had a risk score of three or more. This was not found to be as strongly predictive of the need for insulin (PPV of 44.0%). A higher PPV would be desirable, if the model were to be used to identify a high-risk group subjected to a higher level of care than current guidelines such as more intensive monitoring of glycemic status. Thus, this model is more suitable for use in identifying a low-risk group of women, which could help reduce the number of consultations and health care burden and expense.

Currently, the diagnosis of early GDM before 24 weeks' gestation is being discussed. In Denmark, early screening for GDM has been implemented in weeks 10–20. Therefore, our study population included women diagnosed in early pregnancy (<24 weeks' gestation, 22.0%) and in late pregnancy (≥24 weeks' gestation, 78.0%). We found that women diagnosed <24 weeks' gestation had a higher risk of needing insulin. Therefore, if a consensus is reached regarding screening for early GDM, this risk prediction model should still be applicable to all, as the higher risk of needing insulin in early GDM is accounted for in the model. However, we have not examined if the model's performance is similar in early versus late GDM.

We found some overlap between risk factors for GDM used in the screening criteria, and risk factors for needing insulin included in our model (family history of diabetes and pregestational obesity). The predictive power of prior history of GDM and fetal macrosomia were not examined, as they were not relevant for nulliparous women. However, we did find parity to be predictive of needing insulin. Future studies could try to develop separate risk prediction models for nulliparous and multiparous women including variables related to previous pregnancies, as this may improve the PPV.

To our knowledge few studies have tried to develop a risk prediction model for the need for insulin [11–21]. Of these not all have been successful [12,13]. Some have focused on women diagnosed with GDM in early pregnancy [14,15], and only the study by Barnes et al. [11] used a method similar to the one used in the present study.

Barnes et al. [11] succeeded in making a model with a high predictive power consisting of seven dichotomized clinical and biochemical variables, based on data from a large study population and subsequently validated externally. The predictors of insulin treatment were: maternal age >30 years, family history of diabetes, prepregnancy BMI $\geq$ 30 kg/m^2, prior history of GDM, early diagnosis of GDM < 24 weeks gestation, fasting venous blood glucose level ≥5.3 mmol/L and HbA1c at diagnosis ≥5.5%. Similar to our study, the model by Barnes et al. was able to identify a group of women likely to require only diet treatment (0–1 predictors), but they were also able to identify a high-risk group of women likely to commence insulin treatment during pregnancy (6–7 predictors) with a high PPV (87.6%) and specificity (99.4%).

However, they did not report the performance of their model on the women with two to five predictors present, and they suggest a close monitoring of all women with two or more predictors present only allocating 24.3% of women to a less intensive surveillance program. The model by Barnes et al. also had a low sensitivity (9.3%) and NPV (69.9%), because many women with a higher predictor score remained on diet treatment only.

In addition to this, the application of the model suggested by Barnes et al. is limited to countries which routinely include measurement of fasting blood glucose at the OGTT, as this glucose value is included in the model. Since there is no unified evidence-based protocol for the screening of GDM, the national diagnostic guidelines and procedures for OGTT varies among countries. Some countries, including Denmark, have not yet included measurement of fasting blood glucose in relation to the OGTT for the diagnosis of GDM.

All of the studies mentioned above which attempted to develop a risk prediction model on the need for insulin either did not include the 2-h glucose level at a 75-g OGTT [14–17], or did not find it significantly associated with insulin treatment [11–13,18,19]. In our study,

the 2-h glucose level at the OGTT was the only glucose variable available routinely, and we found that it was independently associated with the need for insulin.

Multiple studies have examined potential variables independently associated with the need for insulin [26–29], and some found a significant association with the 2-h glucose level at the OGTT [26,27]. Koning et al. [27] examined different cut-off values for the 2-h glucose level and found that the association with insulin treatment was considerably stronger at glucose levels ≥9.4 mmol/L (OR 1.93, 95% CI 1.20, 3.11). In addition, Wong et al. [26] found that the 2-h glucose level was significantly associated with the likelihood of commencing insulin treatment when included as a continuous variable. They reported that for every 1.0 mmol/L increase in glucose level, the OR for needing insulin increased by 1.24 (95% CI 1.07, 1.43). Such findings support the use of the 2-h glucose level as a predictive variable on the need for insulin. However, both studies [26,27] concluded that the fasting blood glucose was more predictive of the need for insulin treatment than the 2-h glucose level at the OGTT. Thus, the predictive power of the 2-h glucose level on the need for insulin is still unclear, but our study suggests that it could be an important alternative predictor in countries which do not routinely measure the fasting blood glucose at the OGTT.

In general, the applicability of a risk prediction model for commencing insulin treatment in women with GDM is hampered by the heterogeneity in screening procedures and diagnostic threshold for GDM at the OGTT. Barnes et al. [11] used the ADIPS management guidelines [30], which differ considerably from Danish guidelines [22].

Furthermore, prediction models are influenced by the population prevalence of the condition under consideration. Among other things, the prevalence of GDM varies according to ethnicity. Particularly South Asian and Black African women have an increased risk of developing GDM [31,32]. The studies by Du et al. [19] and Lee et al. [20] included predominantly Asian study populations limiting their external validity in European countries. Similarly, in the study by Barnes et al. [11], the population was ethnically diverse with a prominent representation of women of Asian (45.2%), Middle Eastern (27.0%) and African or Pacific Islander origin (5.3%), and only a small proportion of Europeans (22.5%). Barnes et al. found ethnicity to be a significant predictive variable for the need of insulin. However, ethnicity was excluded as a predictor due to the final model's premise of dichotomization. In comparison, our study consisted of a more homogeneous population with primarily Caucasian women (86.9%). The prevalence of GDM in Australia using ADIPS Guidelines was estimated as 13% from 2011–2014 [33], and due to the ethnic composition, it was probably higher in the study by Barnes et al. In comparison, the prevalence of GDM was 4.3% from 2013–2016 at Aarhus University Hospital [9]. In conclusion, the models may not have the same predictive power in other composite populations not represented by the underlying study population.

In Scandinavia there is still no consensus on the diagnosis and management of GDM, but the national guidelines in Norway [34], Sweden [34] and Denmark [22,23] are similar in many ways apart from the addition of fasting blood glucose in Norway and parts of Sweden [34]. In addition to this, the Scandinavian countries generally report a low prevalence of GDM [35], and a comparable ethnic composition [36]. Norway and Sweden both have a higher percentage of foreign-born compared to Denmark, consisting of primarily immigrants from other EU countries and the Middle East, but the percentage is still clearly lower than for example in Australia [36]. Overall, this supports the generalization of our findings to the Scandinavian countries, but may limit applicability to other countries.

As mentioned previously, studies have had varying success in predicting the need for insulin. Pertot et al. [12] and Mendez-Figueroa et al. [13] found that clinical and biochemical variables alone would not be able to predict the need for insulin. Instead, they suggested that compliance to recommended dietary guidelines might be more predictive regarding the need for insulin, but it may be very difficult to monitor and incorporate in a prediction model.

This study is strengthened by the use of dichotomized clinical and biochemical variables already stored as accessible data on pregnant women with GDM, which makes the

model easy to introduce into clinical practice. Furthermore, the inclusion of a large study cohort increases the significance of the findings. We are not able to determine whether any of the women in the diet treated group with a risk score of at least three met the criteria for starting insulin treatment, but failed to receive it. This may have lowered the predictive power of our model.

The study is limited by the risk of overfitting in regression models which could cause testimation bias and affect the generalizability of the model. Furthermore, the generalizability of the model has not been determined through internal and external validation. Undertaking such validation and following with a randomized controlled trial to test the model in the clinic, would allow us to determine whether use of the model in routine clinical practice leads to earlier initiation of insulin, and if this helps reduce adverse pregnancy outcomes. Similarly, we could assess whether insulin is unintentionally delayed for the women categorized as low-risk, and if this has any adverse clinical consequences. To facilitate comparisons to other prediction models, and possibly improve the predictive power, it would also be relevant to include a fasting blood glucose at the OGTT in later studies. Finally, the performance of the model should be tested in late versus early GDM.

5. Conclusions

We report seven predictors of insulin treatment that are available at the time of diagnosis. These variables can be used in a risk prediction model to stratify women with GDM into lower and higher risk categories based on the likelihood of needing insulin. However, before implementing a risk prediction model such as this into routine clinical practice, it needs to be validated and tested in a clinical setting.

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