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Screening for gestational diabetes mellitus – Can we use the 50-g glucose challenge test of the previous pregnancy?

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ABSTRACT

Aim: To assess the association between previous pregnancy glucose challenge test (GCT) result among non-diabetic women and the rate for gestational diabetes mellitus (GDM) in the subsequent pregnancy.

Methods: Retrospective database study in a university affiliated medical center from 2005 to 2017. Women who had a singleton pregnancy and two consecutive deliveries in our medical center were included. GDM diagnosis was based on either National Diabetes Data Group or Carpenter and Coustan criteria. Univariate analysis was followed by multivariate logistic regression.

Results: A total of 31,861 women were included. GDM incidence among the subsequent pregnancies was 2.1% (670 women). Parturients with GDM had higher mean GCT results in their previous pregnancy compared with parturients without GDM (127.5 ± 28 VS. 98.7 ± 24 mg/dl, $p < 0.001$). Women with GDMA2 had higher former GCT results than women with GDMA1 (135.9 ± 28 VS. 125.7 ± 27 mg/dl, $p < 0.001$). Positive association between GCT results in previous pregnancy and rates of GDM in the subsequent pregnancy was noted. Using a GCT value of 107 mg/dl (65th percentile), the area under the receiver-operating curve was 0.79.

Conclusion: GCT results in previous pregnancy is associated with GDM incidence in the subsequent pregnancy. Future prospective studies are warranted to better delineate the best screening approach for this subset of patients.

1. Introduction

Gestational diabetes mellitus (GDM) is one of the most common medical complications of pregnancy, occurring in 6–9% of women in the USA [1,2] and 2–17% in other specific racial and ethnic groups worldwide [3,4]. GDM impacts on both the mother and the fetus; there is a linear relationship between increasing maternal glycemia and perinatal morbid-

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ity [5]. GDM also has long-term health implications: the recurrence rate is about 50% and up to 70% will develop type 2 diabetes within 10 years of delivery [6,7].

Currently, the Royal College of Obstetricians and Gynecologists (RCOG) recommends that all women be assessed for specific risk factors for GDM at the pregnancy booking appointment, and when risk factors exist, women should be offered testing for GDM [8]. However, previous studies from the USA have shown that as many as 50% of women with GDM will be missed if screening for GDM is based on risk factors alone [9]. As such, the U.S. Preventive Services Task Force (2014) recommend screening all pregnant women for GDM at or beyond 24 weeks of gestation [10]. This recommendation is currently endorsed by the most recent American College of Obstetricians and Gynecologists (ACOG) practice bulletin [11].

As it has been demonstrated that there is low compliance to GDM screening guidelines. Hence, many women are not screened and GDM remains underdiagnosed [12] and most pregnancies occur in women who have had at least one previous pregnancy [13,14], we aimed to explore the risk of GDM in a subsequent pregnancy based on glucose challenge test (GCT) results recorded in a previous pregnancy, among non-diabetic women.

2. Material and methods

We conducted a retrospective cohort study using the computerized medical records of a single large obstetric center, between the years 2005 and 2017. Data on demographic and obstetric characteristics as well as data on delivery complications were extracted from the electronic database management software, which is updated during labor and validated periodically by computer systems personnel. Information technologists retrieved the data and constructed the anonymized data file for analysis. Since the data was retrieved from a clinical dataset, which is updated during labor, all women had complete data regarding the targeted outcomes that were reviewed. We included parturients who had two subsequent deliveries within our center, who had a singleton pregnancy with documented GCT results and no diabetes (pre-gestational or gestational) in their first delivery in our center.

Exclusion criteria were any previous pregnancy complicated with GDM, undocumented GCT result in the previous pregnancy, GCT result in previous pregnancy $\geq$140 mg/dl without documented normal oral glucose tolerance test (OGTT), and multiple gestations in either the previous or subsequent pregnancy.

There is controversy as to the recommended modality to screen for GDM [15], yet the current recommendation in Israel by the Israeli society of obstetrics and gynecology is to screen all women with 50 g GCT [16]. Indeed, in Israel all women receive coverage for antenatal care under the National Health Plan and are routinely screened for GDM via GCT between 24 and 28 weeks of gestation: plasma glucose is tested after administration of a 50 g oral glucose load. Women are referred for an OGTT if the plasma glucose concentration one hour later is $\geq$140 mg/dl, or if there are other risk factors for GDM and the test result is $\geq$130 mg/dl. GDM is diagnosed when two or more abnormal values are observed on a 3-h 100 g OGTT using the Carpenter and Coustan criteria [17], or one abnormal value using the National Diabetes Data Group (NDDG) criteria [18]. Since the difference between the two criteria is only in the OGTT interpretation, both criteria were used simultaneously and GDM diagnosis was established if at least one of them was fulfilled. GDM was also diagnosed with a GCT value of 200 mg/dl or higher [19].

GDMA2 was defined as GDM requiring medical therapy either insulin or oral medications, whereas GDMA1 was diagnosed when diet modification was adequate to manage glucose levels.

The primary outcome variable was the incidence of GDM in subsequent pregnancy based on various levels of previous pregnancy GCT results. Secondary outcomes included: mean GCT levels in women with and without GDM, and rates of GDMA1 and GDMA2 based on previous pregnancy GCT.

2.1. *Statistical methods*

Demographic and obstetric background characteristics were compared between parturients with and without GDM at the subsequent pregnancy using appropriate univariate tests. Continuous variables with normal distribution were compared using Student's *t*-test. Non-normally distributed continuous variables, were compared using the Mann-Whitney test. Categorical variables were compared using Chi-Square or Fisher Exact test where appropriate. All analyses were two-sided and a p-value of <0.05 was considered significant.

Multivariate logistic regression was performed to examine the role of previous pregnancy GCT result as an independent risk factor for GDM in the subsequent pregnancy, while controlling for other known risk factors and possible confounders: maternal age, ethnicity, parity, assisted reproductive technology (ART), hypertensive disorder and neonatal gender, neonatal weight at previous pregnancy, and inter-pregnancy interval (IPI). Receiver operating curves (ROC) were constructed to evaluate the sensitivity, specificity, PPV and NPV of GCT values, at previous pregnancy, divided to deciles, and their prediction of GDM at the subsequent pregnancy. Analyses were carried out using SPSS software package version 22 (IBM, Armonk, NY).

Our local institutional ethics committee approved the study in accordance with the principles of the Declaration of Helsinki (IRB approval number: 0117-19-SZMC). Data were obtained anonymously from medical records without direct participation of patients, hence written informed consent was waived.

3. Results

During the study period, 31,861 women met inclusion and exclusion criteria. Of those, 670 (2.1%) had GDM in their subsequent pregnancy; 553 women with GDMA1 (1.7%) and 117 with GDMA2 (0.4%). While 296 women (0.9%) were diagnosed using Carpenter and Coustan criteria, 495 women (1.4%) were diagnosed using NDDG (an overlap of the diagnostic criteria exists). Maternal demographic, obstetric, and neonatal characteristics were compared between parturients with and

Table 1 – Demographic, obstetric and neonatal characteristics of parturients with and without gestational diabetes mellitus during their subsequent pregnancy and their offspring.

		Without GDM during the subsequent pregnancy (N = 31,191	GDM during subsequent pregnancy (N = 670)	P value
Maternal age at previous delivery (Mean ± SD)		26.36 ± 4.85	29.62 ± 5.31	**<0.001**
Maternal age at subsequent delivery (Mean ± SD)		28.64 ± 5.22	32.54 ± 5.76	**<0.001**
Maternal age > 35 years at subsequent delivery, N (%)		3753 (12.0%)	213 (31.8%)	**<0.001**
Grand multiparity (>5 deliveries) at subsequent delivery, N (%)		4081 (13.1%)	195 (29.1%)	**<0.001**
Previous cesarean deliveries at subsequent delivery, N (%)		4098 (13.1%)	177 (26.4%)	**<0.001**
Previous abortions at subsequent delivery, N (%)		8959 (28.7%)	271 (40.4%)	**<0.001**
Assisted reproductive technology at subsequent delivery, N (%)		670 (2.1%)	21 (3.1%)	0.083
Hypertensive disorders of pregnancy* at subsequent delivery, N (%)		449 (1.4%)	27 (4%)	**<0.001**
Inter pregnancy interval, weeks (Mean ± SD)		76 ± 53	107 ± 79	**<0.001**
Neonatal birth weight at previous delivery, grams (Mean ± SD)		3254 ± 461	3343 ± 539	**<0.001**
Neonatal birth weight > 4000 g, N (%)		1402 (4.5%)	58 (8.7%)	**<0.001**
Neonatal birth weight at subsequent delivery, grams (Mean ± SD)		3302 ± 465	3346 ± 498	**0.024**
Neonatal gender at previous delivery, N (%)	Male	16,023 (51.4%)	333 (49.7%)	0.392
	Female	15,168 (48.6%)	337 (50.3%)	
Neonatal gender at subsequent delivery, N (%)	Male	15,911 (51%)	352 (52.5%)	0.434
	Female	15,280 (49.0%)	318 (47.5%)	

SD – standard deviation; GDM – Gestational Diabetes Mellitus.
*A composite of chronic hypertension, gestational hypertension and preeclampsia.

without GDM in the subsequent pregnancy (Table 1). Parturients with GDM in the subsequent pregnancy were significantly older both during the previous and subsequent pregnancies (29.6 ± 5.3 vs 26.4 ± 4.9 and 32.5 ± 5.8 vs 28.6 ± 5.2, respectively, $p < 0.001$ for both), they were of higher grand-multiparity rate (29.1% vs 13.1%, $p < 0.001$) and had higher incidence of hypertensive disorders of pregnancy during the subsequent pregnancy (4% vs 1.4%, $p < 0.001$). In addition, women with GDM in the subsequent pregnancy had significantly longer IPI than women without GDM (107 ± 79 vs 76 ± 53 weeks, $p < 0.001$) and delivered neonates with significantly higher birth weight in the previous and subsequent pregnancies, as compared to women without GDM in the subsequent pregnancy (3343 ± 539 g vs 3254 ± 461 g and 3346 ± 498 g vs 3302 ± 465 g, respectively, $p < 0.001$ for both).

Mean levels of GCT during the previous pregnancy were significantly higher in women with GDM in the subsequent pregnancy as compared to women without GDM in the subsequent pregnancy (127.5 ± 28 VS. 98.7 ± 24 mg/dl, $p < 0.001$). Additionally, mean levels of GCT during previous pregnancy were significantly higher in women with GDMA2 as compared to women with GDMA1 during the subsequent pregnancy (135.9 ± 28 VS. 125.7 ± 27 mg/dl, $p < 0.001$). There was a positive association between GCT results in the previous pregnancy and rates of GDM at the subsequent pregnancy (Fig. 1). The proportion of GDMA2 to GDMA1 also increased with any increment in GCT result's deciles (Fig. S1).

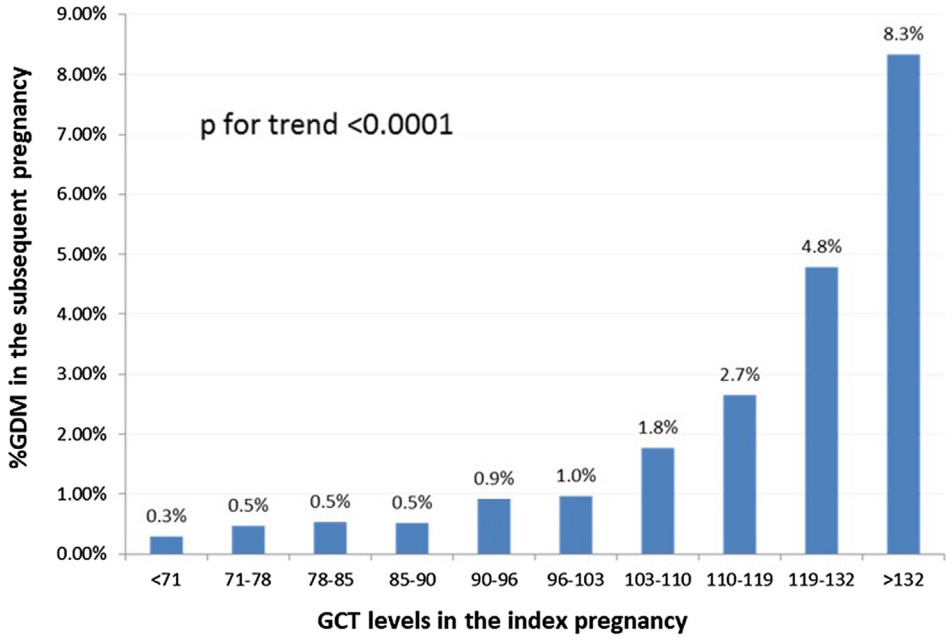
Women whose previous pregnancy GCT result was less than the 65th percentile (107 mg/dl) had a 0.67% incidence of GDM and 0.09% of GDMA2 in the subsequent pregnancy. However, women whose previous pregnancy GCT result was higher than the 80th percentile (≥119 mg/dl) had a 7.0% incidence of GDM and 1.4% of GDMA2 in their subsequent pregnancy. Furthermore, if women whose GCT result was less the 65th, i.e. GCT ≤ 107 mg/dl, (20,767/31,861) were not to be screened again in the subsequent pregnancy, only 20.7% of women with GDM in the subsequent pregnancy would be missed (139/670) and only minority of them would be GDMA2 (18/139, 13%). In order to detect one women with GDMA2, more than 1150 women with previous pregnancy GCT result lower than 107 mg/dl would need to be screened (Table 2).

Of all women diagnosed with GDM when using a GCT value of 107 mg/dl (65th percentile), the area under the ROC was 0.79, suggesting a fair to good accuracy of GCT result in previous pregnancy in predicting GDM in the subsequent pregnancy (Fig. 2). A threshold of 107 mg/dl in previous pregnancy provides a specificity of 67.7% and sensitivity of 78.7% to predict GDM in the subsequent pregnancy. Positive and negative predictive values (PPV and NPV, respectively) were calculated for a threshold of 107 mg/dl. PPV was 4.9% while was NPV 99.3%. Interpretation of the above reveals that only seven of 1000 women with a GCT result of 107 mg/dl or lower in a previous pregnancy, will have GDM in a subsequent pregnancy (see Fig. 3).

Multivariate analysis controlling for confounders revealed that GCT levels in previous pregnancy were independently associated with rates of GDM in the subsequent pregnancy (1.04, 95% CI 1.03–1.04, $p < 0.001$).

4. Discussion

In this retrospective study, we assessed the role of previous pregnancy GCT results for predicting GDM in the subsequent pregnancy in women without GDM or pre-gestational diabetes. It appears that women with GDM in the subsequent pregnancy have higher mean levels of GCT in their previous pregnancy in comparison to women without GDM. Furthermore, we found that the best cut off value to differentiate



GCT – Glucose challenge test; GDM – Gestational diabetes mellitus

Fig. 1 – GDM rate in the subsequent pregnancy by GCT levels recorded in the previous pregnancy.

between women with very low risk of developing GDM and women with higher risk is the 65th percentile, which is 107 mg/dl.

GCT values are of great importance even in women without GDM. Elevated GCT values are associated with higher odds of perinatal morbidity and an increased risk for diabetes in the future [20,21].

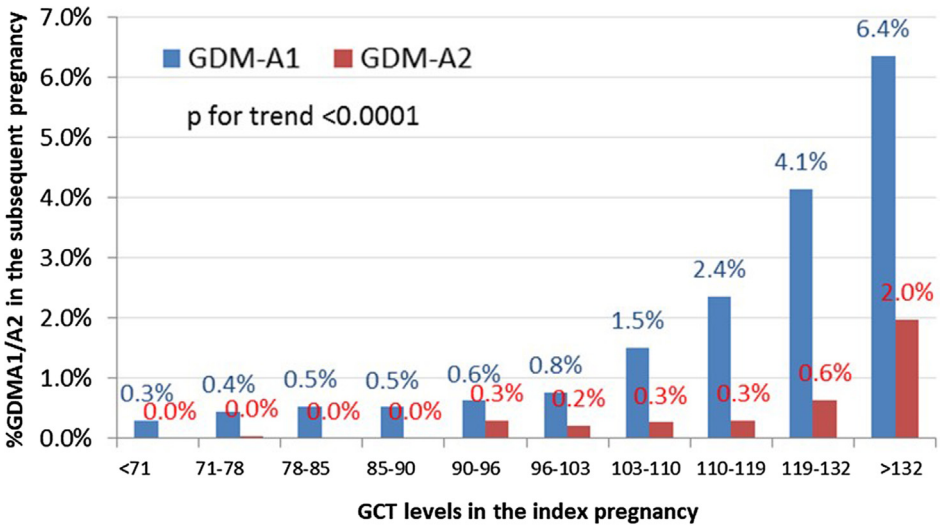
A previous small study that included 705 women without GDM in their previous pregnancy, showed that women who developed GDM in their subsequent pregnancy (n = 38) had higher GCT results in their previous non-diabetic pregnancy than women without GDM in both pregnancies (n = 667). Almost half (44.7%) of the women with new-onset GDM had GCT levels above 133 mg/dl in their previous pregnancy; 84.2% had GCT levels above 119 mg/dl, and all had GCT levels higher than 99 mg/dl [22]. However, given the small sample size, the association between the various GCT levels and the incidence of GDM or the sensitivity and specificity for each GCT result were not calculated.

GDM recurrence rate is about 50% and up to 70% of women with a history of GDM will develop type 2 DM within 10 years after delivery [6,7]. Identifying women at the highest risk of progressing to GDM, and providing them appropriate tools for healthy lifestyle changes may reduce the incidence of

Table 2 – The cumulative rate and number of women with GDM at the subsequent delivery by GCT percentiles from the previous pregnancy.

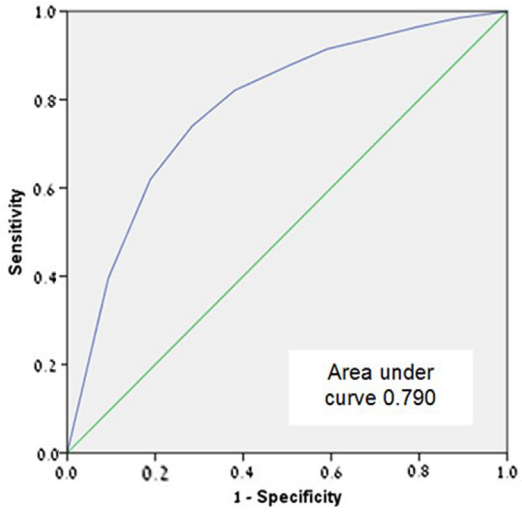
GCT percentile	GCT Value	Number of women	Number of women with GDM	Number of women with GDMA2	Rate of GDM within Cumulative decile	Rate of GDMA2 within Cumulative decile	Cumulative rate of GDM in decile among women with GDM
10	71	3460	10	0	0.29	0.00	1.4
20	78	3009	14	1	0.37	0.02	3.5
30	85	3595	19	0	0.42	0.01	6.3
40	90	2719	14	0	0.44	0.01	8.3
50	96	2736	25	8	0.53	0.06	12
60	103	3914	38	8	0.62	0.09	17.7
65	107	1433	19	1	0.67	0.09	20.7
70	110	1632	35	7	0.77	0.11	25.8
80	119	3049	81	9	0.99	0.13	37.9
90	132	3133	150	20	1.42	0.19	60.3
100	140	3181	265	63	2.14	0.37	100
Total	NA	31,191	670	117	2.14	0.37	

GCT-Glucose Challenge Test; GDM – Gestational Diabetes Mellitus; NA- Non applicable.



GCT – Glucose challenge test; GDM – Gestational diabetes mellitus

Fig. 2 – The ROC for GCT value of 107 mg/dL in previous pregnancy.



GCT – Glucose challenge test; GDM – Gestational diabetes mellitus

Fig. 3 – Roc curve GCT result in previous as a predicator of GDM in the subsequent pregnancy.

GDM, not only to prevent perinatal morbidity but also to improve long-term outcomes for the mother and her child [23].

The importance of GDM and its consequences have led some medical societies to recommend universal screening [10,11] while others still recommend screening based on risk factors [8]. Only recently, two studies were published discussing the risk of GDM and trying to develop or validate a prediction models. In one of these studies, among 6504 Australian women 314 (4.8%) had developed GDM. The chosen prediction model included 8 factors with AUC of 0.79, suggesting a good performance for detection of GDM [24]. In a similar much larger study, Californian birth cohort was utilized, it included 771,140 women for developing a model for prediction of risk of GDM and another 385,568 women for validation. The final model included five well established risk factors and had moderate performance with AUC of 0.73 and 0.71 in the developing cohort and validation cohort, respectively [25].

Although GCT is used as a screening tool in many clinical settings, it is currently applied only to the current pregnancy. It is relatively complex, involves administration of a specific glucose load, an hour waiting period, and the results are not reproducible [26] which is leading to poor compliance [12]. Additionally, studies that included women with risk factors showed that the 50-g glucose challenge holds a pooled sensitivity and specificity of 0.74 and 0.77, respectively (threshold value of 140 mg/dl), indicating that the GCT test will miss approximately 25 percent of cases [27].

Hence, we suggest that once performed in a previous pregnancy, its data may help us to better utilize resources. It may obviate the need for screening in women with a previously low GCT, as the number needed to screen to detect one case of GDM is 150, and the number needed to screen in order to detect one woman with GDMA2 is more than 1150. While women with previous GCT > 119 mg/dl (80th percentile) may benefit from a primary OGTT test in their next pregnancy, as their risk of developing GDM was found to be ≈6.5%.

Our study has several strengths. It is based on a large study population and real time data validation. Antenatal care and screening, childbirth, and postpartum care for mothers and children are uniformly covered by the National Health Insurance limiting the potential for selection bias. A single variable, GCT result in previous pregnancy, provided similar prediction of GDM as models that included several factors.

Our study's limitations include its retrospective design, which potentially overlooks data that might have contributed to our analysis, such as our lack of information regarding smoking and body mass index (BMI), as these are not routinely recorded in our database. Therefore, we could not calculate the influence of BMI on the risk of GDM. Another possible limitation is that we excluded women with GDM in the previous pregnancy that were diagnosed after applying 2 tier screening – one by using the GCT and only than using a diagnostic test. However as noted earlier GCT may miss 25%

of women with GDM, hence it is possible though unlikely that in our cohort women in the second pregnancy had undiagnosed GDM in their first pregnancy.

5. Conclusions

We have shown that GCT results in previous pregnancy are associated with GDM incidence in the subsequent pregnancy. Parturients with GDM in the subsequent pregnancy have higher mean levels of GCT in their previous pregnancy in comparison to women without GDM. Identification of this subset of parturients with low and high risk for GDM in their subsequent pregnancy may promote directed efforts to prevent the unnecessary screening for GDM in the subsequent pregnancy. Future prospective studies are warranted to assess the link between previous pregnancy 75 OGTT result and rates of GDM in the subsequent pregnancy and to better delineate the best screening approach for this subset of patients.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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Contribution of authorship

MR: conception, planning, carrying out, analyzing and writing up the work. RR: conception, planning, carrying out, analyzing and writing up the work. AH: carrying out and writing up the work. RF: analyzing the work. OR: conception, planning, writing up the work. AR: conception, planning, carrying out, analyzing and writing up the work. AS: conception, planning, carrying out, and writing up the work. HYS: conception, planning, carrying out, analyzing and writing up the work.

Details of ethics approval

The study was approved by the local institutional ethics committee in accordance with the principles of the Declaration of Helsinki (IRB approval number: 0117-19-SZMC, July 2018). Data were obtained anonymously from medical records, with no direct participation of patients and hence written informed consent was waived.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.107913.

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