

Research Article

Predictive Value of the Immediate Postpartum Post-Glucola Glucose Test in Gestational Diabetics

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- Persistent glucose intolerance

Abstract

Objective: Assess the utility of the immediate postpartum 75gram, two hours Oral Glucose Tolerance Test (2h-OGTT) to predict delayed glucose normalization in patients with gestational diabetes mellitus (GDM).

Research Design and Methods: Prospective cohort study in women with GDM recruited on Labor and Delivery or the postpartum wards. Patients underwent a 75 gram, 2h-OGTT prior to discharge and were instructed to do so again at six weeks postpartum. Interpretation of glucose values was based on the American Diabetes Association's recommended categories.

Results: Enrollment of 210 patients resulted in 100 subjects completing the study protocol, of which only 45 normalized immediately postpartum. 28 had persistent glucose intolerance at delayed postpartum testing. Post-hoc analysis compared the validity of the immediate postpartum two hour post-glucola (2h-PG) blood glucose value to the delayed 2h-OGTT results. Receiver operator characteristic (ROC) curves identified an optimal threshold for the immediate postpartum OGTT. For GDMA1 patients, an immediate postpartum 2h-PG threshold value of 155 mg/dL gives a negative predictive of 94.1% (P = 0.007), indicating that these patients could forgo delayed postpartum testing. In GDMA2 patients, 2h values of ≥ 200 mg/dL suggested persistent glucose intolerance with a PPV of 70% (P = 0.008).

Conclusion: Adherence of GDM patients to postpartum testing remains poor. Blood sugars do not routinely normalize immediately after delivery. Immediate postpartum 2 hour post-glucola plasma glucose should be further investigated as a promising technique that could potentially identify patients that do not require delayed testing, as well as patients at greatly increased risk of persistent glucose intolerance.

INTRODUCTION

Gestational Diabetes Mellitus (GDM) complicates approximately 200,000 pregnancies in the United States annually. While the immediate clinical implications of GDM include obstetric and neonatal complications, there is a high likelihood for these patients to develop diabetes in the future. Up to one-third of pregnant women diagnosed with GDM will have impaired glucose metabolism or diabetes at their recommended six to twelve weeks postpartum screening [1]. Approximately 15-50% will go on to develop type II diabetes in their lifetime [2]. The American Congress of Obstetricians and Gynecologists (ACOG) and the American Diabetes Association (ADA) have both recommended screening for persistence of diabetes at least six weeks after delivery. Though postpartum screening is

up from 20.7% in 1995 to 53.8% in 2006, overall adherence to this recommendation remains poor despite efforts to improve compliance [3]. The true prevalence of postpartum glucose intolerance may be even higher than what has been reported in the past. A study by Hunt *et al.*, [4] found that women who failed to return for postpartum glucose testing had more severe GDM.

ACOG has recently declared its proposed GDM performance measure as the percentage of women with GDM who complete postpartum screening for type II diabetes [2]. However, effective methods to improve compliance with postpartum screening recommendations remain a challenge. Various reminder systems have been implemented that they have been found to greatly increase postpartum screening rates [5].

There has also been some evidence that supports testing

patients early in the postpartum period, [6-8] based on evidence that the pregnancy-related changes in glucose metabolism in gestational diabetics may resolve soon after delivery. There is an association of suppressed adiponectin and increased placental TNF-alpha in pregnancy, which contributes to the insulin resistant state in women with GDM [9,10]. With the delivery of the placenta, placental TNF-alpha levels rapidly drop to previous non-pregnant levels leading to the resolution of the pregnancy component of the insulin resistant state. Thus, we speculated that the 2h-OGTT may have clinical relevance in the immediate postpartum period and that it may be offered while the patient is still in the hospital. If so, this approach could significantly improve patient compliance with testing. Our hypothesis was that the 2h-OGTT would normalize in the immediate postpartum period in most women.

MATERIALS AND METHODS

This post-hoc analysis combines data from two Institutional Review Board (IRB) approved prospective cohort studies conducted at Naval Medical Center San Diego. Informed consent was obtained from participants, with enrollments taking place between 2005-2008 and 2013-2014. The same protocol was utilized during both time periods – the gap in conducting the study was related to staff reassignments at a military facility.

Subjects were recruited from Labor & Delivery and the postpartum wards. Inclusion criteria were women with GDM who delivered after 35 weeks gestational age. The diagnosis of GDM was made using the two step method: A 50g, 1h-OGTT followed by a diagnostic 100g, 3h-OGTT after an abnormal screening. In patients with a 1h-OGTT value ≥ 200 mg/dL, the diagnostic 3h-OGTT was deferred and the diagnosis of GDM given empirically. Carpenter and Coustan criteria were used for diagnosis with the 3h-OGTT. Exclusion criteria were prior history of type I or II diabetes mellitus (DM), medical conditions requiring long-term steroid treatment in pregnancy, preterm birth at less than 35 weeks gestation, age less than 18 years and greater than four days postpartum. Enrolled patients included both diet controlled GDM (GDMA1) patients and medically managed GDM (GDMA2) patients. As there is no specific guidance as to when to initiate medical therapy, [2] this classification was left to the individual providers as is the routine at this institution. They underwent a 2h-OGTT one to four days after giving birth, typically on the morning of discharge from the hospital. If IV fluids were still being administered, it was ensured that they were not glucose containing. A fasting plasma glucose (FPG) was obtained followed by a 75 gram oral glucose load. The post-glucola plasma glucose was obtained two hours later (2hPG). Subsequently the study participants were instructed to repeat the 2h-OGTT at approximately six weeks postpartum visit. The patients were then reminded again at six weeks postpartum via a telephone call, text message, or email – the option for preferred method of contact was provided to the patient. If the test was not completed, up to two additional reminders were given. These immediate and delayed postpartum values were then compared.

Primary outcome measure was that a normal immediate 2h-OGTT would predict a normal delayed 2h-OGTT. Using this primary outcome, with the power of the study set at 80% and

statistical significance with a two-tailed test P value of 0.05, three hundred patients would need to complete the protocol. During the 2005 to 2008 period only 60 patients completed the study protocol. When the study was resumed in 2013, enrollment was high in the first year but compliance continued to be poor despite multiple mechanisms in place to remind patients to complete their delayed 2h-OGTT. Assuming a consistent rate of patient accrual and completion, an additional six years would be required to complete the study. Additionally, fewer patients normalized immediately postpartum than we anticipated, making the clinical utility of the immediate 2h-OGTT limited. Abandoning our hypothesis and further continuation of the study, we obtained permission from the IRB to combine the data from both studies and performed a post-hoc analysis of the combined data set seeking information that could have clinical utility for the immediate post-partum testing of women with GDM.

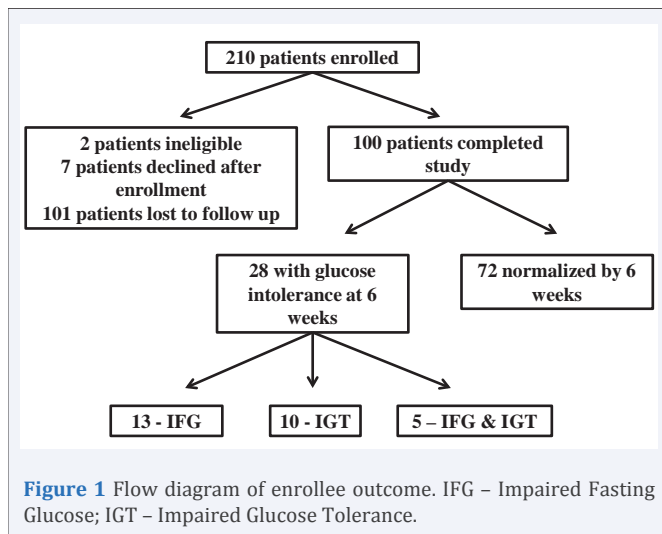
Initially both the FPG and 2h PG values were included; however we observed that the FPG during the immediate postpartum test added little additional information. Only three patients out of 100 had impaired fasting glucose (IFG) without concomitant impaired glucose tolerance (IGT). Of those three, only one remained abnormal at delayed postpartum testing. Therefore, in the immediate postpartum test we focused solely on the 2h PG values in the assessment of the test's utility. This approach has been previously termed a modified glucose tolerance test [7].

Data analysis was performed using an online statistics package (www.MedCalc.org) to find the sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), relative risk (RR), *p* value and confidence interval (CI) of the postpartum tests. Receiver Operator Characteristic Curves (ROC's) were created using Stata version 13 (Stata Corp, College Station TX). A two-tailed *p* value of less than 0.05 was considered significant.

RESULTS

Full demographic data for the 2005-2008 phase of the study was only available for patients who completed the study – there were no notable characteristics. For 2013-2014 enrollees, population characteristics were unremarkable [Table 1]. In the earlier study, 110 patients were enrolled, 4 declined after enrollment leaving 106 who did the immediate postpartum test - of which 60 patients completed the study protocol. In the 2013-2014 study, 100 were enrolled, 2 were found ineligible, 3 declined after enrollment, and 95 patients did the immediate postpartum test – of which 40 patients completed the study protocol. Between the two studies, a total of 210 patients were enrolled, 201 tested immediately postpartum of which 101 were lost to follow up. A total of 100 patients completed the study protocol, 28 of them exhibiting persistent glucose at delayed testing. No patients were diagnosed with DM.

See figure 1 for flow diagram of enrollee outcome. The delayed postpartum testing period was recommended at 6-12 weeks, but the completed tests spanned a period from four weeks to 44 weeks postpartum with a mean of nine weeks. Though the recommended time period for completion is 6-12 weeks postpartum, this is based on the presumption that normalization



has occurred and that any abnormalities at that point indicate persistent glucose intolerance. Therefore, even outliers at 44 weeks postpartum were included as they could still be relied upon to indicate normalization vs. persistence of glucose intolerance.

The immediate postpartum 2h PG values were compared to the delayed postpartum OGTT using the American Diabetes Association's criteria for the 75 gram 2h-OGTT. An immediate 2h post glucoala value < 140 mg/dL was considered test negative, and any abnormalities at the delayed postpartum test to include IFG, IGT, or DM, were grouped together as "condition positive". The NPV was 82.2 %, PPV 36.4%, sensitivity 71.4 %, specificity 51.4%, with RR 2.05 (CI 0.997 - 4.19, P = 0.051). Only 45 patients tested negative. There were eight false negatives identified by the immediate 2h PG and 35 false positives. 57 patients were correctly identified by their immediate postpartum test. We chose not to separate results by which day postpartum the immediate testing was done, to prevent the unintended results of altering the timing of discharge.

Noting that our data demonstrated the pregnancy's impact on glucose metabolism persisted in the immediate period we sought to establish a more appropriate cut-off for the immediate postpartum 2h-PG. An ROC was developed [Figure 2] AUC 0.678 to analyze all immediate 2h-PG in reference to the six week postpartum outcome (normal/abnormal). In this cohort, a 2h-PG level of less than 155 mg/dL provided the optimal predictive cut-off value to distinguish normal levels in the immediate period with a NPV of 83 %, PPV of 45%, Sensitivity of 64.3%, Specificity of 69.4%, and RR of 2.7 (CI 1.39-5.23, P=0.003). Using this new cut-off resulted in improving the false positive rate from 35 to 22 while the false negative rate was only 10 for the cohort of 100 patients. 68 patients were correctly identified in the immediate postpartum period.

GDMA1 and GDMA2 patients were then separated and ROC's were developed for each of these subgroups. For the 50 GDMA1 patients, a 2h-PG cut-off value of 155 mg/dL was established [Figure 3], (AUC 0.726).34 had a 2h PG <155 mg/dL of which only two remained abnormal at six weeks (5.9%). Both of these patients had IFG at delayed testing, with a fasting glucose of 100 and 103. Of the 16 patients with 2hPG \geq 155 mg/dL, seven

patients (43.8%) had persistent glucose intolerance. Using <155 mg/dL in GDMA1 patients gave a NPV of 94.1%, PPV of 43.8%, Sensitivity of 77.8%, Specificity of 78%, and RR of 7.4(CI 1.73-31.86, P = 0.007). In this subgroup of 50 patients, the immediate postpartum PG value < 155mg/dL resulted in 9 false positives, two false negatives, and correct identification of 39 patients.

For the GDMA2 subgroup, the optimal predictive value was a 2h PG of 200 [Figure 4] (AUC 0.627).Of the 50 GDMA2 patients, 10 had a 2hPG \geq 200. Seven of those 10 (70%) had persistent glucose intolerance. Of the 40 patients with 2hPG<200, 12 additional patients (30%) exhibited persistent glucose intolerance. This value yielded a NPV of 70%, PPV of 70%, Sensitivity of 36.8%, Specificity of 90.3%, and RR of 2.33 (CI 1.25-4.35, P = 0.008). In this subgroup of 50 patients, the immediate postpartum PG value < 200mg/dL resulted in 3 false positives, 12 false negatives, and correct identification of 35 patients.

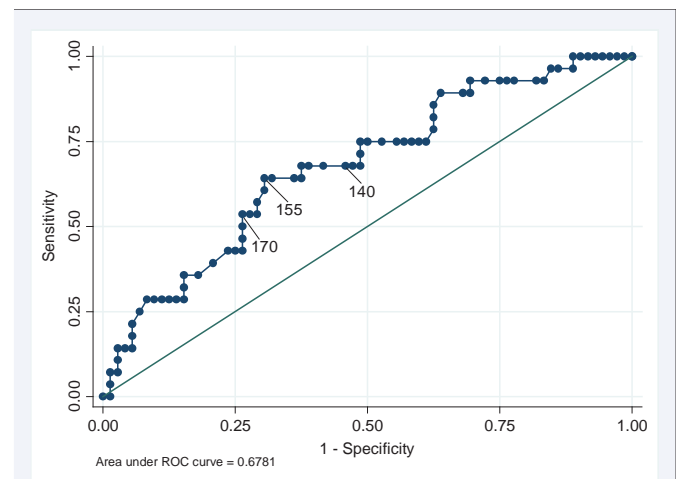


Figure 2 Receiver Operator Curve, all patients (n=100) - Comparison of 2hr post-load value at immediate GTT to 6 week postpartum GTT (normal/abnormal).

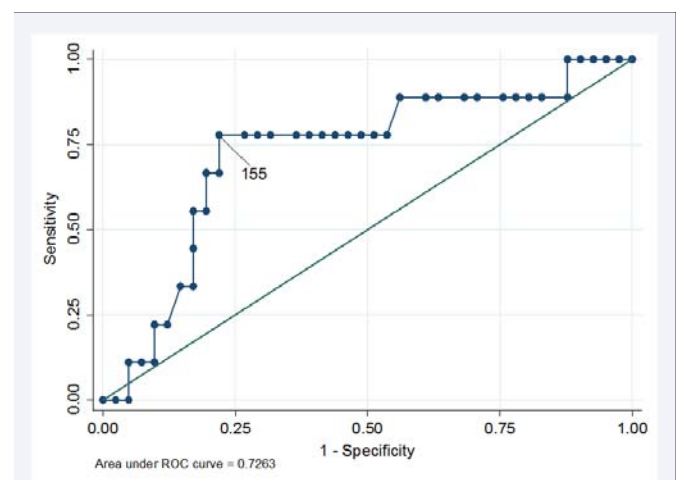


Figure 3 Receiver Operator Curve, GDMA 1 patients (n= 50) - Comparison of 2hr post-load value at immediate GTT to 6 week postpartum GTT (normal/abnormal).

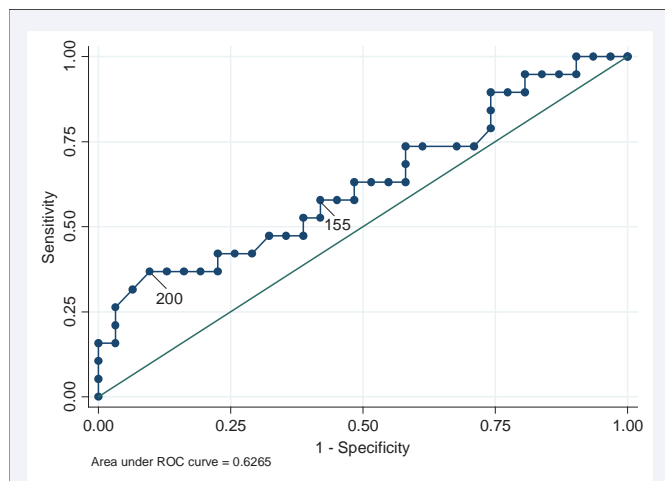


Figure 4 Receiver Operator Curve, GDMA 2 patients (n= 50) - Comparison of 2hr post-load value at immediate GTT to 6 week postpartum GTT (normal/abnormal).

CONCLUSION

Our data indicate pregnancy-related changes continue to exert effects on glucose metabolism in the immediate postpartum transition. An immediate postpartum modified 2h-OGTT in which only a 2hr post-glucola serum value is obtained could be performed, and with redefined parameters could be utilized for risk stratification. This could determine who could opt out of delayed postpartum testing who would benefit from closer follow up.

Our study is thus far the largest in the literature to look at immediate postpartum glucose testing during the period of postpartum hospitalization. We found that fewer patients normalized immediately postpartum than initially than we anticipated, limiting the clinical utility of the immediate 2h-OGTT using traditional cut-off values. Strengths in study design include the practicality of testing women during the postpartum hospitalization, diverse demographic base, and novel approach to utilization of the collected data after abandonment of the initial hypothesis and study. Its weaknesses include the spread of enrollment encompassing two separate time periods, demographic data limited to subjects who completed the study protocol, and abandonment of the initial hypothesis.

There is a well-established need for continued improvement in postpartum follow-up of gestational diabetics. Our study was similarly prey to poor compliance with aforementioned recommendations. It adds to the body of literature demonstrating testing is problematic and transitions into why this effort is important. Attempts at reminder systems are helpful, [5] but not sufficient, thus a variety of other possible methods are under investigation. Prediction models from antenatal factors have not yet been found successful [11]. Coordinating efforts with primary care physicians is a promising possibility but remains to be realized [12].

Another approach to improvement in this field would explore the pathophysiology of Gestational Diabetes. Though not yet fully understood, there is increasing interest in role of adipokines in

the regulation and pathophysiology of the disease process, as well as prognostic implications [13,14]. With relatively short half-lives, most should clear from the parturient rather rapidly. This reasoning accounts for the interest in early post-partum testing, which has thus far indicated it may prove useful [6,7], including a small pilot study which performed 2h-GTTs on postpartum day two [8]. That particular study showed that a 2h-OGTT performed on postpartum day two had a low false-negative rate and may be a viable alternative [8]. The study was limited by its size, with only 26 subjects completing the study. Another study compared glucose testing within six days postpartum to testing the same cohort six weeks postpartum [6]. Though designed to look at glucose intolerance in patients with and without complications it also indicated persistence of pregnancy effects of glucose intolerance in the early postpartum period, with 75% of their GDM patients exhibiting glucose intolerance in that time frame. Another study utilized a modified 2h-OGTT which did not include the FPG to test 39 GDM women at 4 days post-partum, of which 77% had a normal test. This number increased to 90% at 6 to 12 weeks after delivery [7]. The largest study in the early postpartum period evaluated 270 women with GDM with OGTT

Table 1: Patient Demographics.

Demographic	Completed 6wk Postpartum GTT (n = 100)
Sponsor Status	
Active Duty	21
Dependent	79
Age	
<30y/o	49
≥30y/o	51
Ethnicity	
African American	7
Asian	21
Caucasian	41
Hispanic	14
Other	17
GDM status	
GDMA1	50
GDMA2	50
Family Hx	
Present	64 (64)
None or unknown	36 (36)
BMI status	
<25	44 (44)
>25	56 (56)
Mode of Delivery	
Vaginal	68 (68)
Cesarean	32 (32)
Parity	
P1	49 (49)
P2	32 (32)
P3-5	19 (19)

on day seven and six week's post-partum. They found that 70% of women were normoglycemic on day seven after giving birth, and this increased to 75% at six week's [15]. These initial studies indicate that there is a rapid return to baseline non-pregnant glycemic metabolism for most women early post-partum period.

Our results indicate that GDMA1 patients with a 2h-PG value of less than 155 mg/dL have a very low risk of persistent glucose intolerance (5.9%). Given this low risk it may be reasonable to forgo the six week postpartum OGTT in these patients. They should still follow the recommendations for retesting every three years to screen for the development of overt diabetes. However, the GDMA1 patients with 2h-OGTT values of 155 mg/dL or greater carried a significant risk of remaining glucose intolerant (43.8%) and should be counseled to follow up on the six week 2h-OGTT to determine their status.

Meanwhile, there may also be a use for immediate postpartum testing in GDMA2 patients. The positive predictive value of 70% of a 2hPG \geq 200 mg/dL for persistent abnormal glucose tolerance makes a case for strongly recommending continuation of lifestyle modifications and emphasizing the importance of formal testing at six weeks. However, as these only encompassed 20% of the GDMA2 patients, the number to test would be high, so this would need to be weighed against the cost of less than half of these patients being identified by current testing methods.

Using a two-tiered approach of immediate testing followed by six week 2h-OGTT for GDMA1 patients with 2h-PG value of 155 mg/dL or greater could be used as a risk stratification method for improving identification of patients that are likely to develop DM in the near future [16]. Few patients who enrolled ultimately declined, indicating that a fasting test during the immediate postpartum time period is likely to be well-received by patients. Our strategy for immediate postpartum testing would reduce the number of GDMA1 patients needing to undergo testing at the six week postpartum period by two-thirds. This could make manageable more intensive follow-up efforts in a population at high risk for glucose intolerance or continued diabetes in the postpartum period. However, implementing such a strategy would require a larger long term prospective follow on study to validate its implications.

Disclaimer: The views expressed in this presentation are those of the authors and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, or the U.S. Government.

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Dr. Steffanie Owens is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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