Comparison of 2-Hour Oral Glucose Tolerance Test and Hemoglobin A1C in the Identification of Pre-Diabetes in Women with Infertility and Recurrent Pregnancy Loss

Clinical Medicine Insights: Reproductive Health
Volume 13: 1–5

DOI: 10.1177/1179558119831280

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ABSTRACT

RESEARCH QUESTION: Does hemoglobin A1C (HbA1C) predict pre-diabetes (pre-DM) in a population of women with infertility and/or recurrent pregnancy loss (RPL), when considering the 75 g, 2-hour oral glucose tolerance test (2h GTT) as the gold standard?

DESIGN: Retrospective study of 242 patients with infertility or RPL presenting to a university-affiliated reproductive endocrinology and infertility clinic between January 2012 and December 2016 who underwent screening for disorders of glucose metabolism with a 2h GTT. The prevalence of pre-DM as defined by HbA1C 5.7% to 6.4% and 2h GTT values of 140-199 mg/dL, and predictive values of HbA1C for the identification of pre-DM when compared with 2h GTT, were calculated and compared.

RESULTS: Of 242 patients, 188 (77.7%) women had both HbA1C and 2h GTT performed. Of these, 89 (47.3%) tested positive for pre-DM by one or both methods. Of 89 patients, 14 (15.7%) had both an abnormal 2h GTT and an abnormal HbA1C. Only 6 out of 89 (6.7%) patients tested positive for pre-DM by an abnormal 2h GTT in the setting of a normal HbA1C result. Conversely, 69 of these 89 patients (77.5%) tested positive for pre-DM by an abnormal HbA1C in the setting of a normal 2h GTT. The prevalence of pre-DM, as defined by 2h GTT, was 10.6% (20/188) (95% CI, 6.6-16.0), compared with a prevalence of 44.1% (83/188) (95% CI, 36.9-51.6) when pre-DM was defined by HbA1C alone. When the 2h GTT was considered the gold standard for the identification of pre-DM, the negative predictive value (NPV) of HbA1C compared with 2h GTT was 94.3% (95% CI, 88.0-97.9), whereas the positive predictive value (PPV) of HbA1C compared with 2h GTT was only 16.9% (95% CI, 9.5-26.7).

CONCLUSIONS: Although a normal HbA1C was highly predictive of a normal 2h GTT, the two tests demonstrate poor agreement in the identification of pre-DM in women with infertility and/or RPL. Hemoglobin A1C is superior to the 2h GTT as an initial screening test for pre-DM in this population, since it identified a substantial number of women who would otherwise remain undiagnosed in the setting for a normal 2h GTT alone. However, the long-term clinical relevance of an elevated HbA1C in this population needs to be better defined.

KEYWORDS: pre-diabetes, glucose metabolism, infertility, recurrent pregnancy loss, hemoglobin A1C, 2-hour oral glucose tolerance test

RECEIVED: December 20, 2018. **ACCEPTED:** January 23, 2019.

TYPE: Original Research

FUNDING: The author(s) received no financial support for the research, authorship, and/or publication of this article.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Introduction

There are over 30 million Americans living with diabetes (DM), with a projected 7 million still undiagnosed.[1] An additional 84.1 million have pre-diabetes (pre-DM), a metabolic state which is at high risk of developing into DM if untreated, making it a critical clinical intervention point for the prevention of DM.[1]

Pre-diabetes affects approximately 17.9% of all reproductive-age women[2] and can significantly impact fertility. Women with certain reproductive disorders are at increased risk for disorders of glucose metabolism, especially those with polycystic ovary syndrome, also known as PCOS. In women with PCOS, the prevalence of pre-DM is 35% and the prevalence of DM can be as high as 10%.[3] Recurrent pregnancy loss (RPL) has also been associated with uncontrolled DM and elevated hemoglobin A1C (HbA1C) values. In light of these findings, the American College of Obstetricians and Gynecologists (ACOG) and the American Society for Reproductive Medicine (ASRM) have issued specific guidelines regarding screening for disorders of glucose metabolism. ACOG recommends screening all women with PCOS for abnormal glucose metabolism with a 75g, 2-hour oral glucose tolerance test (2h GTT),[4] while ASRM recommends measuring a HbA1C during the diagnostic work-up for women with RPL.[5]

Multiple screening methods for diagnosing pre-DM exist, each with its own benefits and drawbacks. As a dynamic test that evaluates the ability to regulate glucose metabolism after an oral glucose load, the 2h GTT is often considered to be the

"gold standard" for diagnosis of DM and pre-DM with an abnormal result, referred to as "impaired glucose tolerance," signifying the presence of pre-DM.[6] The 2h GTT represents the ability to process an oral glucose load and rises earlier in the disease process than fasting plasma glucose (FPG),[7] allowing for earlier detection of abnormal glucose metabolism. However, the 2h GTT can be cumbersome for patients. It requires at least 8 h of fasting, an initial fasting blood draw, followed by ingestion of a 75 g oral glucose load that many patients may find unpalatable, and then a second blood draw after a 2-h waiting period. These additional requirements represent a significant inconvenience and may lead to delayed diagnosis of abnormal glucose metabolism because of increased time commitment and preparation required by the patient.

Another screening method is FPG, the concentration of which depends on hepatic glucose secretion.[6] Although inexpensive and easy to administer, like the 2h GTT it requires patients to fast for at least 8 h prior to blood draw and can vary significantly depending on illness, medications, prolonged fasting, exercise, and stress.[7]

A third commonly used screening test is HbA1C, which quantifies the amount of glycated hemoglobin in the blood and is a measure of long-term glycemic exposure.[7] HbA1C has been shown to correlate with the risk of development of microvascular disease such as diabetic retinopathy[8] and has less within-person variation than FPG and 2h GTT values, which can fluctuate significantly from day to day.[7] Measuring a HbA1C value does not require the patient to fast and only requires a single blood draw, making it more convenient for both the patient and provider. However, there are a number of hematologic conditions in which HbA1C may not give an accurate result.[7,9] For example, hemoglobinopathies may interfere with the HbA1C interpretation, as well as any condition in which red blood cell turnover is increased, such as hemolytic anemia, chronic malaria, and acute blood loss.[9]

Although multiple screening methods for the diagnosis of pre-DM exist, no specific recommendation as to which test is best for the identification of pre-DM in women with infertility and RPL has yet been established. The objective of this study was to determine whether HbA1C accurately predicts the presence of pre-DM in this patient population when considering 2h GTT as the gold standard.

Materials and Methods

A retrospective chart review was performed for patients presenting to a university-affiliated reproductive endocrinology and infertility clinic between January 2012 and December 2016 who underwent screening for disorders of glucose metabolism with a 2h GTT. Additional glucose testing including HbA1C and FPG levels was recorded for each patient, when available, and when performed within 3 months of the 2h GTT. We included patients who were at least 18 years of age and less than 45 years of age. Patients with known diagnoses of abnormal glucose metabolism were excluded, as were patients outside of the designated age range. Demographic data collected for the patients included age, body mass index (BMI), and infertility diagnosis or diagnoses. A diagnosis of PCOS was determined based on the Rotterdam Criteria established in 2003, which requires two of the following: oligo- or anovulation, clinical and/or laboratory evidence of hyperandrogenism, and polycystic ovaries on ultrasound, with the exclusion of other etiologies for these findings.[10] Unexplained infertility was defined as the inability to conceive despite a normal basic infertility evaluation. Women with RPL were defined as those with a history of two or more failed clinical pregnancies.

Pre-DM was defined by any of the following: FPG 110-125 mg/dL, 2h GTT 140-199 mg/dL, or HbA1C 5.7-6.4%. DM was defined as one of the following: FPG $\geq$ 126 mg/dL, 2h GTT $\geq$ 200 mg/dL, or HbA1C $\geq$ 6.5%.

Statistical analysis was performed using both SAS 9.4, SAS Institute Inc., Cary, NC, and Microsoft Excel, Version 14.7.6. A P value of less than .05 was considered significant. Confidence intervals (CIs) were determined using Clopper-Pearson methodology. Cohen's kappa co-efficient was calculated to assess level of agreement between 2h GTT and HbA1C in the identification of pre-DM. This study was approved by the Rutgers Health Sciences Institutional Review Board (Newark, NJ).

Results

During this time period, a total of 242 women met inclusion criteria. Of these, 211 out of 242 (87.2%) women had more than one screening method for abnormal glucose metabolism performed; 188 out of 242 (77.7%) women had a HbA1C done either at the time of the 2h GTT or within 3 months of the 2h GTT.

The demographics of these patients are shown in Table 1. PCOS was the single most common diagnosis, affecting 147 out of 242 (60.7%) patients screened with a 2h GTT during this time period. The mean age of those screened was 33.7 $\pm$ 5.7 years and mean BMI was 31.6 $\pm$ 8.0 kg/m^2 (Table 1). Mean HbA1C and 2h GTT values did not differ significantly among patient subgroups (Table 2).

Of the 188 patients with both an HbA1C and 2h GTT result available, 89 (47.3%) tested positive for pre-DM with either an elevated HbA1C, an abnormal 2h GTT, or both an abnormal HbA1C and an abnormal 2h GTT. Of these 89 patients, 14 (15.7%) had both an abnormal 2h GTT and an abnormal HbA1C. Only 6 out of 89 (6.7%) patients tested positive for pre-DM by an abnormal 2h GTT in the setting of a normal HbA1C result. Conversely, 69 of these 89 patients (77.5%) tested positive for pre-DM by an abnormal HbA1C in the setting of a normal 2h GTT (Figure 1).

The prevalence of pre-DM, as defined by 2h GTT, was 10.6% (20/188) (95% CI, 6.6-16.0, P=0.27), compared with the prevalence of 44.1% (83/188) (95% CI, 36.9-51.6, P < .0001) when pre-DM was defined by HbA1C alone. When using the 2h GTT as the gold standard for a true diagnosis of pre-DM,

Table 1. Patient characteristics.

PATIENT CHARACTERISTIC	ALL PATIENTS (N = 242)	PATIENTS WITH BOTH 2H GTT AND HBA1C (N = 188)
Age (years) (mean ± SD)	33.7 ± 5.7	32.8 ± 5.7
BMI (kg/m^2) (mean ± SD)	31.6 ± 8.0	31.5 ± 7.6
PCOS	148/242 (61.0%)	116/188 (61.7%)
RPL	19/242 (7.9%)	12/188 (6.38%)
Unexplained	29/242 (11.8%)	15/188 (8.0%)
Other diagnosis	46/242 (19.0%)	45/188 (23.9%)

Abbreviations: BMI, body mass index; PCOS, polycystic ovary syndrome; RPL, recurrent pregnancy loss; 2h GTT, 2-hour oral glucose tolerance test.

Table 2. Average HbA1C and 2h GTT values in patient subgroups.

	ALL	PCOS	UNEXPLAINED	RPL
HbA1C, mean ± SD (%) (range)	5.7 ± 0.61 (4.8-12.3)	5.7 ± 0.50 (4.8-12.3)	5.7 ± 0.30 (4.8-12.3)	5.7 ± 0.30 (4.8-12.3)
2h GTT, mean ± SD (mg/dL) (range)	102 ± 35 (38-236)	97.5 ± 40.8 (38-236)	97.8 ± 17.6 (38-236)	97.8 ± 65.6 (38-236)

Abbreviations: HbA1C, hemoglobin A1C; PCOS, polycystic ovary syndrome; RPL, recurrent pregnancy loss; 2h GTT, 2-hour oral glucose tolerance test.
Groups are not mutually exclusive.

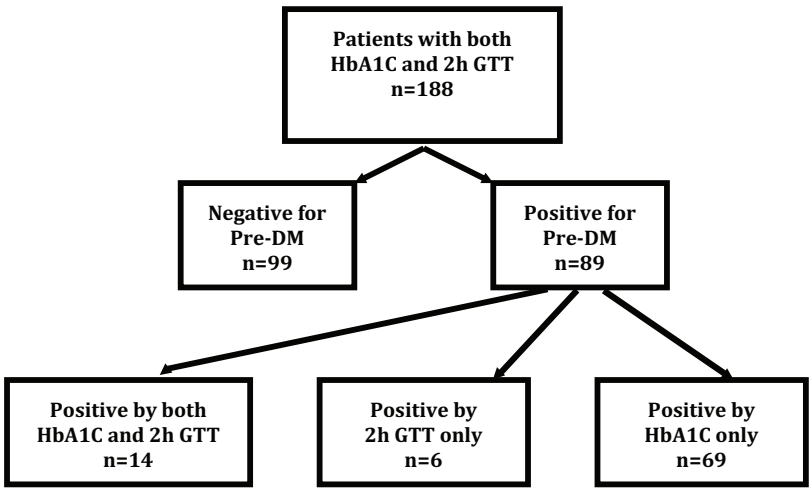

Figure 1. Flow chart of patient subgroups. HbA1C indicates hemoglobin A1C; Pre-DM, pre-diabetes; 2h GTT, 2-hour oral glucose tolerance test.

the sensitivity of HbA1C in the identification of pre-DM in the overall study population was 70% (95% CI, 45.7-88.1). The sensitivity of HbA1C was similar when broken down by diagnosis of PCOS or RPL (Table 3). The specificity of HbA1C in the overall population screened was 58.9% (95% CI, 51.1-66.4), meaning that of those women with normal glucose metabolism as defined by a normal 2h GTT, approximately 59% also had a normal HbA1C (Table 3).

In addition, when the 2h GTT was considered the gold standard, the negative predictive value (NPV) of HbA1C compared with 2h GTT was 94.3% (95% CI, 88.0-97.9). This high NPV was seen among all of the patient subgroups. However, the positive predictive value (PPV) of HbA1C compared with 2h GTT was only 16.9% (95% CI, 9.5-26.7). This low PPV was seen across all patient subgroups. Cohen's kappa statistic across all categories showed poor agreement between the two tests across all patient subgroups (Table 3).

Discussion

Although multiple methods exist to screen for disorders of glucose metabolism,[6] there are no recommendations regarding which screening method is superior in women with infertility

Table 3. Prevalence of pre-diabetes as defined by 2h GTT and HbA1C.

POPULATION	PREVALENCE (2H GTT) %	PREVALENCE (HBA1C) %	SENSITIVITY %	SPECIFICITY %	NPV%	PPV%	COHEN'S KAPPA
All (n = 242) (95% CI)	10.6 (6.6, 16.0)	44.1 (36.9, 51.6)	70.0 (45.7, 88.1)	58.9 (51.1, 66.4)	94.3 (88.0, 97.9)	16.9 (9.5, 26.7)	0.121 (2.1, 22.1)
PCOS (n = 148) (95% CI)	11.0 (6.0, 18.1)	39.0 (30.1, 48.4)	69.2 (38.6, 90.9)	64.8 (54.8, 73.8)	94.4 (86.4, 98.5)	19.6 (9.4, 33.9)	0.161 (1.7, 30.4)
RPL (n = 19) (95% CI)	25.0 (5.5, 57.2)	58.3 (27.7, 84.8)	66.7 (9.4, 99.2)	44.4 (13.7, 78.8)	80.0 (28.4, 99.5)	28.6 (3.7, 71.0)	0.077 (0.0, 51.4)
Unexpl. (n = 29) (95% CI)	5.9 (0.1, 28.7)	58.8 (32.9, 81.6)	100.0 (2.5, 100.0)	43.8 (19.8, 70.1)	100.0 (59.0, 100.0)	10.0 (0.3, 44.5)	0.084 (0.0, 24.8)

Abbreviations: CI, confidence interval; HbA1C, hemoglobin A1C; NPV, negative predictive value; PCOS, polycystic ovary syndrome; PPV, positive predictive value; RPL, recurrent pregnancy loss; 2h GTT, 2-hour oral glucose tolerance test.
Sensitivity, specificity, predictive values, and Cohen's kappa co-efficient of HbA1C when compared with 2h GTT.

and/or RPL. To our knowledge, the present study is the first to compare glucose metabolism screening tests for the identification of pre-DM in women with infertility and RPL. Our objective was to compare HbA1C, a fast and convenient method for diagnosing pre-DM in the general adult population, with the 2h GTT, a less convenient and more time-consuming test widely considered to be the gold standard for diagnosis of abnormal glucose metabolism.

We found a significant difference between HbA1C and 2h GTT in the identification of pre-DM in a population of women with infertility and/or RPL. The prevalence of pre-DM in our study population as defined by HbA1C was 44.1% (95% CI, 36.9-51.6, $P < .0001$), which was significantly higher than the prevalence of pre-DM as defined by a 2h GTT, which was only 10.6% (95% CI, 6.6-16.0, $P = .027$). This indicates that a substantial number of patients with an abnormal HbA1C will have a normal 2h GTT result. This finding holds true regardless of patient diagnosis (Table 2).

However, our results also indicate that HbA1C shows a high level of agreement with 2h GTT in detecting the absence of pre-DM, regardless of infertility diagnosis. When using the 2h GTT as the gold standard test for identification of pre-DM, the NPV of HbA1C in detection of pre-DM was 94.3%. In contrast, the PPV of HbA1C compared with 2h GTT was only 16.9%. This was seen among all patients regardless of diagnosis. These findings, in addition to the low Cohen's kappa co-efficient, demonstrate that for the diagnosis of pre-DM in women with infertility and RPL, HbA1C and 2h GTT are not equivalent.

Women presenting for evaluation and management of infertility and RPL represent a unique clinical opportunity. Many women living with pre-DM have no symptoms and are undiagnosed, which makes screening high-risk women incredibly important. Early identification of patients with pre-DM is a critical intervention point because it has been shown that individuals with HbA1C of 6% to 6.5% have a 5-year risk of 25% to 50% of developing DM.[11] Establishing a diagnosis of abnormal glucose metabolism during the reproductive years allows for implementation of risk-lowering strategies, including lifestyle modifications and pharmacologic management, prior to development of significant adverse health consequences associated with DM. Patients with infertility and RPL may also be particularly motivated to make lifestyle changes not only to improve their own health, but also to increase their chances of conceiving.

Although the American Diabetes Association (ADA) established in 2013 that HbA1C is an acceptable method for the diagnosis of pre-DM in the general population,[12] the efficacy of HbA1C in identifying patients with pre-DM remains controversial.[13–15] Multiple studies performed on specific subpopulations have consistently found the 2h GTT to be superior to HbA1C in the diagnosis of pre-DM.[14,15] A study performed in 2012 compared HbA1C to 2h GTT in the diagnosis of pre-DM during post-partum screening for women with a history of gestational diabetes mellitus (GDM).[14] In

this population of women, the 2h GTT identified a higher prevalence of pre-DM when compared with HbA1C as a screening test (45.9% compared with 19%, respectively).[14] A cross-sectional study of 671 women with PCOS also demonstrated that HbA1C was insufficient for the identification of pre-DM when compared with 2h GTT, with HbA1C identifying only 19 of 76 patients with pre-DM.[15]

Other studies performed in the general population also found a significant number of patients with abnormal glucose tolerance testing that had normal HbA1C levels[16,17] (Lee et al., 2018). An Italian study found the concordance between glucose tolerance testing and HbA1C in the identification of pre-DM to be only 54%. Among patients with normal HbA1C values of <5.7%, 33% demonstrated impaired glucose tolerance and/or impaired fasting glucose.[16] A Korean study of 3203 young adults ages 20 to 29 also found that HbA1C showed poor agreement with FPG in the identification of pre-DM (Lee et al., 2018)[19]; almost 5% of patients with impaired fasting glucose would have been misclassified as normoglycemic if screened by HbA1C alone. This study determined an optimal HbA1C cutoff level of 5.5% in the identification of impaired glucose tolerance, substantially lower than the 5.7% used by the ADA. Taken together, these findings suggest that HbA1C may not be the optimal method for abnormal glucose tolerance screening, although this may differ in specific sub-populations.

Although our study identified a higher prevalence of pre-DM with HbA1C testing when compared with the 2h GTT, it should be noted that the long-term effects of this observation have not yet been established. It is unclear if identification of pre-DM by HbA1C alone, and potential interventions as a result of this screening test, would truly lead to a decreased incidence of DM in this population. An additional limitation of our study is its retrospective nature. Furthermore, our study only includes patients screened with both a 2h GTT and HbA1C and does not include patients screened with fasting glucose alone, HbA1C alone, or 2h GTT alone. Thus, this population may not be representative of a broader population of women with infertility and RPL. Our study also does not account for additional factors that may influence HbA1C values, including anemias due to iron deficiency (which may falsely elevate HbA1C) or other causes.[18] However, our study did include patients across the spectrum of infertility diagnoses, in addition to those with RPL, and our findings did not vary significantly between patient subgroups.

In summary, our study demonstrates poor agreement between HbA1C and 2h GTT in the identification of pre-DM in women with infertility and RPL, including those with PCOS-associated infertility. In the population studied, HbA1C was superior to 2h GTT as an initial screening test for the identification of pre-DM. However, the clinical significance of an abnormal HbA1C in the setting of a normal 2h GTT remains unclear. Prospective studies are needed to ascertain long-term health risks in infertile women, who despite normal glucose tolerance testing, are diagnosed with pre-DM on the basis of an abnormal HbA1C.

Author's Note

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Author Contributions

AJS, ECH, PGM and SSM contributed to the experimental design, implementation and manuscript writing. DA contributed to statistical analysis and result interpretation.

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