Trends in Screening for Diabetes in Early Pregnancy in the United States

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Trends in Screening for Diabetes in Early Pregnancy in the United States

A Master’s Thesis Presented

By

Gianna Wilkie, MD

Submitted to the Faculty of the University of Massachusetts Morningside Graduate School of Biomedical Sciences, Worcester

in partial fulfillment of the requirements for the degree of

Master of Science

December 23, 2021

Clinical Investigation
Trends in Screening for Diabetes in Early Pregnancy in the United States

A Master’s Thesis Presented

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Gianna Wilkie, MD

The signatures of the Master’s Thesis Committee signify completion and approval as to style and content of the thesis.

______________________________________________________________________________

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______________________________________________________________________________

Heidi Leftwich, DO, Member of Committee

The signature of the Dean of the Morningside Graduate School of Biomedical Sciences signifies that the student has met all master’s degree graduation requirements of the school.

______________________________________________________________________________

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Dean of the Graduate School of Biomedical Sciences

Master of Science in Clinical Investigation

December 23, 2021
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There are many individuals that have supported me throughout my career and have contributed to my growth as a clinician researcher. I would like to specifically thank my TRAC committee members including Dr. Heidi Leftwich, Dr. Tiffany Moore Simas, and Dr. Tony Nunes. All of my committee members have helped me develop further research skills and serve as a constant resource when I have questions or need guidance. I would also like to thank Dr. Goldberg for his help in developing my grant writing skills, and support of the maternal fetal medicine fellows in the MSCI program. I would also like to thank Kate Lapane for being instrumental in helping the maternal fetal medicine fellowship trainees navigate classes and the MSCI program around our clinical schedules.
Abstract
Objective: To characterize current diabetes screening practices in the first trimester of pregnancy in the United States, evaluate patient characteristics and risk factors associated with early diabetes screening, and compare perinatal outcomes by early diabetes screening.

Methods: This was a retrospective cohort study of US medical claims data from patients diagnosed with a viable intrauterine pregnancy who presented for care before 14 weeks of gestation without pre-existing pre-gestational diabetes from the IBM MarketScan® database for the period of January 1, 2016, to December 31, 2018. Univariate and multivariate analyses were used to evaluate clinical factors and perinatal outcomes.

Results: There were 400,588 pregnancies identified as eligible for inclusion, with 18.0% of women receiving early screening for diabetes. Of those with laboratory order claims, 53.1% had hemoglobin A1c, 30.0% fasting glucose, and 16.9% oral glucose tolerance tests. Compared to women who did not have early diabetes screening, those that did were more likely to be older, obese, have a history of gestational diabetes, chronic hypertension, polycystic ovarian syndrome, hyperlipidemia, and a family history of diabetes. In adjusted logistic regression, history of gestational diabetes (aOR 3.99, 95% CI 3.73-4.26) had the strongest association with early diabetes screening. Early diabetes screening irrespective of the screening result was also associated with adverse perinatal outcomes including a higher rate of cesarean delivery, preterm delivery, gestational hypertension, pre-eclampsia, and gestational diabetes.

Conclusion: First trimester early diabetes screening was mostly commonly performed by hemoglobin A1c evaluation, and women that underwent early diabetes screening regardless of the result were more likely to experience adverse perinatal outcomes.
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**Introduction**

Gestational diabetes mellitus (GDM) is a relatively common complication affecting 6 to 8% of pregnancies every year in the United States, with upwards of 1 in every 8 pregnancies worldwide depending on the effectiveness of screening approaches and subsequent interventions.1-4 Women with GDM have higher rates of adverse perinatal outcomes and are more likely to develop pre-eclampsia, have a preterm delivery, need a cesarean delivery, and develop type 2 diabetes mellitus later in life than women who do not develop this condition.5-9 Furthermore, the offspring of women with GDM are at increased risk for macrosomia, neonatal hypoglycemia, birth trauma, stillbirth, metabolic syndrome and diabetes in adulthood.10-13

Despite adverse intergenerational outcomes associated with GDM, this condition is not detected until approximately 28 weeks of gestation, as routine screening for GDM is currently performed between 24 to 28 weeks of gestation. This screening, as recommended by American College of Obstetricians and Gynecologists guidelines, does not allow significant time for pregnancy related interventions.14 The commonly employed detection methods rely on oral glucose challenge tests which are time-consuming and difficult for patients to coordinate and undergo. Early identification of GDM may be initiated by obstetric providers based on additional diabetic risk factors such as obesity or a history of GDM in a prior pregnancy; however, there is no consensus on the optimal method of screening for the early detection of GDM leading to inconsistencies in clinical practice.14-17

The objectives of this study were to characterize current diabetes screening practices in the first trimester of pregnancy in the United States, evaluate patient characteristics and risk factors associated with early diabetes screening, and compare perinatal outcomes by early diabetes screening.
Methods

Study Population and Design
This was a retrospective cohort study of US medical claims data from patients diagnosed with an intrauterine pregnancy that received screening for diabetes in the first trimester of pregnancy defined as less than 14 weeks of gestation from the IBM MarketScan® database for the period of January 1, 2016, to December 31, 2018. This data range was selected due to the increased accuracy of gestational age dating after implementation of ICD-10 codes. The IBM Marketscan® is the largest available source of medical claims data in the US, capturing over 245 million unique patients since 1995 with over 40 million patients captured annually in recent years. The medical claims are sourced from employer-based commercial and Medicare Part D plans. The claims capture the full spectrum of care across physician office visits, hospital stays, pharmacy dispensing, and specialty/carve-out care. Patients can be followed over time and between sites of care. The coding of medical claims conforms to insurance industry standards including use of designated claims forms, ICD-9/10 diagnosis codes and procedure codes, Current Procedural Terminology (CPT) codes, Health Care Financing Agency (HCFA) Common Procedure Coding System (HCPCS) codes, cost information, and de-identified patient and provider codes. Pharmacy claims data allow for longitudinal tracking of medication fill patterns and changes in medications. These data include the National Drug Code (NDC), Generic Product Identifier (GPI), drug name, dosage form, drug strength, fill date, days of supply, and cost information.

From the IBM MarketScan® database, a population-based cohort of patients with an intrauterine pregnancy were identified using the following selection criteria: patients were between the ages of 15 to 44 with an intrauterine pregnancy as defined by International Classification of Diseases, 10th Revision (ICD-10) codes (Supplementary Table 1). Women with
a molar pregnancy, ectopic pregnancy, or pre-existing diagnosis of pre-gestational diabetes including Type 1 and Type 2 diabetes were excluded.

Assessment of Exposures and Outcome

Our primary outcome included the prevalence of early diabetes screening, defined as any individual or combination of hemoglobin A1c, oral glucose tolerance test (50 gram, 75 gram, or 100 gram glucose test), or fasting plasma glucose. The type of test was identified by current procedural terminology (CPT) codes. Hemoglobin A1c was identified by CPT codes 83036 and 83037, while fasting plasma glucose was identified by code 82947. Oral glucose tolerance tests were identified by CPT codes 82950, 82951, and 82952.

Clinical factors associated with early diabetes screening were assessed as possible exposure variables. Clinical history factors including age, region, body mass index, history of GDM in a prior pregnancy, chronic hypertension, polycystic ovarian syndrome (PCOS), obesity, hyperlipidemia, and a family history of diabetes were collected as identified by ICD-10 codes (Supplementary Table 1).

Pregnancy-related maternal outcomes were compared among women who received early diabetes screening and women who did not receive early diabetes screening. Maternal outcomes including cesarean delivery, preterm delivery, gestational hypertension, pre-eclampsia/HELLP syndrome, and GDM were included. All maternal outcomes were identified by ICD-10 codes.

Statistical Analysis

Categorical variables were summarized as raw numbers with percentage, while continuous variables were summarized with the mean (standard deviation) where appropriate. Women who underwent early screening for diabetes were compared to women who did not undergo early screening using Chi-square or student t-tests as appropriate. Individual risk factors
were examined as predictors of prompting early diabetes screening and were assessed using logistic regression. Odds ratios and 95% confidence intervals are reported. Analyses are adjusted for variables including obesity, history of GDM and chronic hypertension, and family history of diabetes, which is consistent with prior literature. An additional regional level analysis was performed to identify possible geographic variation in screening practices for diabetes in early pregnancy. The regions within this database included northeast, north central, south, west and unknown. The northeast region included Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont, New Jersey, New York, and Pennsylvania, while the north central region included Illinois, Indiana, Michigan, Ohio, Wisconsin, Iowa, Kansas, Minnesota, Missouri, Nebraska, North Dakota, and South Dakota. The south region included Washington D.C., Delaware, Florida, Georgia, Maryland, North Carolina, South Carolina, Virginia, West Virginia, Alabama, Kentucky, Mississippi, Tennessee, Arkansas, Louisiana, Oklahoma, and Texas, while the west included Arizona, Colorado, Idaho, Montana, Nevada, New Mexico, Utah, Wyoming, Alaska, California, Hawaii, Oregon, Washington, and Puerto Rico.

Two-sided P values <0.05 were considered statistically significant in all analyses. Statistical analyses were completed using STATA/IC 16.1 (College Station, Texas). The study was deemed exempt from Institutional Review Board approval from the University of Massachusetts Chan Medical School at Worcester, MA, USA given the use of deidentified publicly available data.

**Results**

The study population consisted of 400,588 women with intrauterine pregnancies during the study period. Overall, the included pregnant women were approximately 30.0 years old,
12.5% obese, and 0.9% with a history of GDM. Of all included women, 18.0% received diabetes screening in the first trimester. Among women who received early screening, 53.1% had screening with hemoglobin A1c, 30.0% with fasting glucose, and 16.9% with an oral glucose tolerance test. Among women that had early glucose screening tests completed, 85.2% had a 1-hour 50-gram oral glucose tolerance test, while 5.3% were had a 2-hour 75-gram oral glucose tolerance test. The type of diabetes screening test did not vary significantly by region of the country, with hemoglobin A1c being the most common screening test in each region and oral glucose tolerance test being the least utilized.

Women that underwent diabetes screening in the first trimester were significantly different from women that did not undergo early screening. Women who had first trimester diabetes screening were more likely to be older (30.8 vs. 29.8, p<0.001), have diagnosed obesity (21.6% vs. 10.5%, p<0.001), have a history of gestational diabetes (2.6% vs. 0.6%), chronic hypertension (6.3% vs. 3.8%), polycystic ovarian syndrome (3.9% vs. 1.7%, p<0.001), hyperlipidemia (3.0% vs. 1.4%, p<0.001), and a family history of diabetes (1.8% vs. 0.8%) (Table 1).

When assessing clinical factors associated with first trimester screening, history of GDM (aOR 3.99, 95% CI 3.73-4.26), history of chronic hypertension (aOR 1.30, 95% CI 1.25-1.34), family history of diabetes (aOR 2.25, 95% CI 2.10-2.42), and obesity (aOR 2.25, 95% CI 2.20-2.30) were all associated with an increased odds of undergoing early diabetes screening, with history of GDM being the strongest risk factor for early screening (Table 2).

Women who had first trimester diabetes screening had significantly higher rates of adverse perinatal outcomes compared to women who did not have first trimester screening. Women with early screening were more likely to have a cesarean delivery (9.2% vs. 7.3%,
p<0.001), gestational hypertension (10.6% vs. 8.0%, p<0.001), pre-eclampsia/HELLP syndrome (6.8% vs. 5.2%, p<0.001), and GDM (9.9% vs. 5.1%, p<0.001) compared to women without screening (Table 3). There was also a statistically significant difference in rates of preterm delivery (4.3% vs. 4.0%, p<0.003), however this likely does not represent a clinically significant difference.

**Discussion**

This study found that approximately 1 in 5 pregnant privately insured women had first trimester early diabetes screening and that hemoglobin A1c was the most common approach to early screening. Additionally, women that underwent early diabetes screening regardless of the result were more likely to experience adverse perinatal outcomes, likely due to the clinical characteristics and risk factors that prompted early diabetes screening.

While approximately 20% of pregnant women in this study cohort underwent early screening, this is likely less than should be screened based on the prevalence of clinical risk factors such as obesity. It is estimated that 29% of pregnant women in the United States are obese, and this represents only one clinical risk factor that should prompt screening. However, the study cohort had an overall obesity rate of 12.5% likely reflecting underestimation of this clinical condition due to the low sensitivity of claims based diagnostic codes for obesity. With the rising maternal age in pregnancy, increasing rates of obesity, and greater prevalence of type 2 diabetes mellitus in the general population, screening for diabetes in the first trimester will become more commonplace. It is therefore imperative that optimal screening methods are employed to detect the population at highest risk.
Hemoglobin A1c was the test used most frequently for early diabetes screening, which is not unexpected given the ease of completion of this testing compared to oral glucose tolerance tests or fasting glucose values. The critical cut off value for hemoglobin A1c in the first trimester of pregnancy that correlates with either development of GDM or other adverse perinatal outcomes is not entirely known, and it is possible that hemoglobin A1c may not be predictive of perinatal outcomes. One possible explanation for the heavy reliance on hemoglobin A1c in early pregnancy is that providers prefer a simple serum test offered with initial prenatal laboratory evaluation rather than an oral glucose tolerance test due to the convenience associated with test completion. Further evaluation into why hemoglobin A1c is the most ordered test and its true impact as a sole screening test for early diabetes in pregnancy is needed.

The significant difference in clinical demographics among women who were tested in the first trimester is in accordance with risk-factor based guidelines outlined by the American College of Obstetricians and Gynecologists. However, risk factor screening has scored poorly in predicting GDM. Selective screening by risk factors for GDM has previously been shown to have relatively low sensitivity yet seems to be used predominantly in the US population. Further evaluation into the early screening and the ability to predict adverse perinatal outcomes is needed to determine modes of early intervention that may lead to maternal and neonatal benefit. In the current study, the act of obtaining early screening was associated with significant adverse perinatal outcomes when compared to those who were not screened, likely due to the numerous risk factors prompting screening.

*Strengths and Limitations*

Our study strengths include the large sample size from a national database, which represents a large obstetric cohort. Women within the study were cared for by midwives,
generalists, and maternal-fetal medicine specialists in both private and academic settings, suggesting that these findings highlight generalizable practice patterns.

This study is limited by its reliance on CPT codes and diagnostic billing codes to correctly identify the patient population of interest and perinatal outcomes. The validity of utilizing ICD-10 codes to identify pregnancies and obstetric outcomes has been previously shown to be accurate, although reliance on ICD-10 codes may lead to misclassification of diabetes screening. Additionally, the results are limited to only women with private insurance, as it does not include women without insurance or those with public insurance. This limitation impacts the generalizability of these results to the entire United States population. An obstetric cohort including both private and publicly insured would likely yield even more significant risk factor differences and poorer outcomes associated with those risk factors. However, little is known about the current early diabetes screening practices in a publicly insured population.

In conclusion, approximately 1 in 5 privately insured pregnant women in the United States had first trimester diabetes screening, with hemoglobin A1c being the most frequently performed test. The variation in the current practices of early diabetes screening in pregnancy from the recommended standard of care highlight the need for improved early detection methods that rely on easy to obtain serum biomarkers. Further research into optimal screening for diabetes in the first trimester is needed.
References


Table 1. Demographic and Clinical Characteristics Comparison Among Women with and without Early Diabetes Screening in Pregnancy

<table>
<thead>
<tr>
<th></th>
<th>Early Diabetes Screening (n=71,973)</th>
<th>No Early Screening (n=328,615)</th>
<th>P -value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>30.80 (5.31)</td>
<td>29.83 (5.47)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Region of US</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northeast</td>
<td>14,149 (21.72)</td>
<td>50,987 (78.28)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>North Central</td>
<td>14,726 (16.85)</td>
<td>72,674 (83.15)</td>
<td></td>
</tr>
<tr>
<td>South</td>
<td>29,284 (15.77)</td>
<td>156,379 (84.23)</td>
<td></td>
</tr>
<tr>
<td>West</td>
<td>13,745 (22.21)</td>
<td>48,133 (77.79)</td>
<td></td>
</tr>
<tr>
<td>Pregravid Body Mass Index &gt;=30 kg/m²</td>
<td>15,522 (21.6)</td>
<td>34,403 (10.5)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>History of Gestational Diabetes</td>
<td>1,832 (2.6)</td>
<td>1,962 (0.6)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>History of Chronic Hypertension</td>
<td>4,517 (6.3)</td>
<td>12,494 (3.8)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Family History of Diabetes</td>
<td>1,282 (1.8)</td>
<td>2,467 (0.8)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Polycystic Ovarian Syndrome</td>
<td>2,818 (3.9)</td>
<td>5,618 (1.7)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>2,141 (3.0)</td>
<td>4,499 (1.4)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

All data are represented as n(%) or mean(standard deviation). P values <0.05 are considered statistically significant.
Table 2. Logistic Regression for Early Diabetes Screening Based on Clinical Risk Factors

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted Odds Ratio (95% CI)</th>
<th>Adjusted Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of GDM</td>
<td>2.05 (2.00-2.12)</td>
<td>3.99 (3.73-4.26)</td>
</tr>
<tr>
<td>History of Chronic HTN</td>
<td>1.69 (1.64-1.76)</td>
<td>1.30 (1.25-1.34)</td>
</tr>
<tr>
<td>Family History of Diabetes Mellitus</td>
<td>2.40 (2.24-2.57)</td>
<td>2.25 (2.10-2.42)</td>
</tr>
<tr>
<td>Obesity</td>
<td>2.35 (2.30-2.40)</td>
<td>2.25 (2.20-2.30)</td>
</tr>
</tbody>
</table>

All data are reported as odds ratio (95% confidence interval). Adjusted odds ratios are adjusted for all other variables in the model including obesity, history of GDM, history of chronic hypertension, and family history of diabetes.
Table 3. A Comparison of Perinatal Outcomes Among Women with and without Early Diabetes Screening in Pregnancy.

<table>
<thead>
<tr>
<th></th>
<th>Early Diabetes Screening (n=71,973)</th>
<th>No Early Screening (n=328,615)</th>
<th>P -value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cesarean Delivery</td>
<td>6,642 (9.23)</td>
<td>23,853 (7.26)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Preterm Delivery</td>
<td>3,071 (4.27)</td>
<td>13,056 (3.97)</td>
<td>&lt;.0003</td>
</tr>
<tr>
<td>Gestational Hypertension</td>
<td>7,619 (10.59)</td>
<td>26,371 (8.02)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Pre-eclampsia/HELLP syndrome</td>
<td>4,878 (6.78)</td>
<td>16,974 (5.17)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Gestational Diabetes Mellitus (GDM)</td>
<td>7,126 (9.90)</td>
<td>16,685 (5.08)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

All data are reported as n(%). P values <0.05 are considered statistically significant.
Supplementary Table 1. ICD-10 Codes for Cohort Selection and Demographic History

<table>
<thead>
<tr>
<th>ICD-10 Codes</th>
<th>Identifying Pregnant Women in the First Trimester</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z3A, Z3A.0, Z3A.00, Z3A.01, Z3A.08, Z3A.09, Z3A.1, Z3A.10, Z3A.11, Z3A.12, Z3A.13, Z3A.14, Z3A.15, Z3A.16, Z3A.17, Z3A.18, Z3A.19, Z34.01, Z34.81, Z34.91, O09.91, O09.11, O09.A1, O09.211, O09.291, O09.31, O09.41, O09.511, O09.521, O09.611, O09.621, O09.71, O09.811, O09.821, O09.891, O09.91</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>History of Gestational Diabetes</th>
<th>Z86.32</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of Hypertension</td>
<td>O10, O10.0, O10.01, O10.011, O10.012, O10.013, O10.019, O10.02, O10.03, O10.1, O10.11, O10.111, O10.112, O10.113, O10.119, O10.12, O10.13, O10.2, O10.21, O10.211, O10.212, O10.213, O10.22, O10.23, O10.3, O10.31, O10.311, O10.312, O10.313, O10.319, O10.32, O10.33, O10.4, O10.41, O10.411, O10.412, O10.413, O10.419, O10.42, O10.43, O10.9, O10.91, O10.911, O10.912, O10.913, O10.919, O10.92, O10.93</td>
</tr>
</tbody>
</table>

| Family History of Diabetes      | Z83.3  |
| Polycystic Ovarian Syndrome (PCOS) | E28.2  |
| Hyperlipidemia                  | E78, E78.0, E78.00, E78.01, E78.1, E78.2, E78.3, E78.4, E78.41, E78.49, E78.5, E78.6, E78.7, E78.70, E78.71, E78.72, E78.79, E78.8, E78.89, E78.9 |
| Preterm delivery                | O60.1, O60.12, O60.13, O60.14, O60.10X0, O60.12X0, O60.13X0, O60.14X0 |
| Cesarean delivery               | O66.41, O75.82, O82, Z38.01, Z38.31, Z38.62, Z38.64, Z38.66, Z38.69 |
| Gestational Hypertension        | O13, O13.1, O13.2, O13.3, O13.4, O13.5, O13.9 |