First Trimester Fasting Hyperglycemia and Adverse Pregnancy Outcomes

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Objective: The HAPO study found strong associations between higher levels of maternal glucose at 24-32 weeks, within what is currently considered normoglycemia and adverse pregnancy outcomes. Our aim was to evaluate the associations between first trimester fasting plasma glucose level and adverse pregnancy outcomes.

Research Design and Methods: Charts of all patients who delivered at our hospital between 6/2001 and 6/2006 were reviewed. Only subjects with singleton pregnancy and a recorded first trimester fasting glucose level were included. Women with pregestational diabetes, fasting glucose level>105mg/dL or delivery<24 weeks were excluded. Fasting glucose levels were analyzed in seven categories, similar to the HAPO study. The main outcomes were development of gestational diabetes mellitus (GDM), large for gestational age (LGA) neonates and/or macrosomia and primary cesarean section. Multivariate logistic regression analysis was used; significance<0.05.

Results: 6129 women had fasting glucose test at median of 9.5 weeks. There were strong graded associations between fasting glucose level and primary outcomes: the frequency of GDM development increased from 1.0% in the lowest glucose category to 11.7% in the highest, adjusted odds ratio [AOR], 11.92; 95% confidence interval [CI], 5.39-26.37. The frequency of LGA and/or macrosomia increased from 7.9% to 19.4%, AOR 2.82 (95%CI 1.67-4.76). Primary cesarean section rate increased from 12.7% to 20.0%, AOR 1.94 (95%CI 1.11-3.41).

Conclusion: Higher first trimester fasting glucose levels, within what is currently considered a nondiabetic range, increase the risk of adverse pregnancy outcomes. Early detection and treatment of women at high risk for these complications might improve pregnancy outcome.
Women with gestational diabetes mellitus (GDM) are at increased risk for adverse perinatal and maternal outcomes including macrosomia, cesarean section, birth trauma and later Diabetes Mellitus. The Toronto tri-hospital gestational diabetes project(1) and the Hyperglycemia and Adverse Pregnancy Outcome Research Group(2) studied the relationship between plasma glucose levels, less severe than overt GDM, and pregnancy outcomes. They found graded relation between increasing levels of fasting, 1-hour and 2-hour plasma glucose obtained on oral glucose-tolerance testing at 24-32 weeks, and a wide variety of adverse pregnancy outcomes including increased birth weight, primary caesarean section, neonatal hypoglycaemia and preclampsia.

Using fasting plasma glucose as a screening test for adverse pregnancy outcomes early in gestation offers some advantages compared to glucose challenge tests. Glucose tolerance tests are poorly reproducible, time consuming, expensive, require extensive patient preparation, inconvenient to administer and unpleasant for the patient and in pregnant women vomiting is a common problem. Fasting plasma glucose is easy to administer, well tolerated, inexpensive, reliable, reproducible and has been reported to vary little throughout gestation(3). However, there is no universally agreed definition for normal fasting glucose level in pregnancy. In pregnant women, similar to the nonpregnant state, fasting plasma glucose above 125 mg/dL is considered diagnostic for diabetes mellitus(4). In nonpregnant adults impaired fasting glucose is diagnosed with fasting glucose levels of 100-125 mg/dL(4). However there is no definition for impaired fasting glucose during pregnancy: in the 3 hours 100 gram oral glucose tolerance test (OGTT) a fasting glucose value above 105 mg/dL was considered abnormal by the NDDG criteria(5); Whereas the Carpenter and Coustan criteria for the diagnosis of GDM set the normal fasting glucose, in the OGTT, to less than 95mg/dL(6).

Detection of women at higher risk for adverse pregnancy outcomes early in pregnancy is a desirable goal because interventions such as diet, medication, and exercise may be applied earlier and have a positive effect on maternal and fetal outcomes(7-9). Therefore we wanted to evaluate, retrospectively, the associations between fasting glucose level in the first trimester, within what is currently considered normoglycemia, and adverse pregnancy outcomes.

RESEARCH DESIGN AND METHODS

The protocol was approved by the institutional review board for human investigation at Carmel Lady Davis Medical Center which is part of Clalit health maintenance organization (HMO). The study was also approved, for computerized laboratory data retrieval, by the committee for health policy research in the central administration of Clalit HMO. This was a retrospective study on deliveries that took place in Carmel Lady Davis hospital from June 2001 to June 2006. During this period we used a computerized medical record in the labor and delivery ward. The computerized record includes demographic data (including woman's name, identification number, age and maternal self report of prepregnancy weight and height), obstetric data (including gravity, parity, previous cesarean section and estimated last menstrual period (LMP) based on both date of LMP and early ultrasound examination), delivery data (including gestational age at delivery and mode of delivery) and neonatal data (including neonatal weight and apgar score). This data
was extracted into a computerized database (Access database, Microsoft, Seattle, WA).

There is no uniform worldwide guidelines for screening and diagnosis of gestational diabetes mellitus(10). In Israel, the ministry of health recommends universal testing for fasting glucose level at the first prenatal care visit and universal 50 gram glucose challenge test (GCT) at 24-28 weeks of gestation(11). According to these guidelines, women with abnormal GCT of 140mg/dL or more should undergo a 3 hour 100 gram oral glucose tolerance test (OGTT).

The Israeli National Health Insurance Law provides universal health services to every resident. Carmel Lady Davis hospital is part of the Clalit health services which is the largest health maintenance organization (HMO) in Israel. Using the unique identity number assigned to all Israeli residents and through the central laboratory computer of Clalit HMO, we extracted the results of all glucose blood tests that were done during the study period for patients who gave birth in our hospital and had Clalit HMO insurance. Gestational age for the various glucose tests was calculated using the date of last menstrual period and the date of glucose test. Venous plasma glucose concentration was determined by the glucose oxidase method in Clalit laboratories.

Included in this study. Women with pregestational diabetes mellitus, fasting glucose level more than 105mg/dL or delivery at less than 24 weeks of gestation were excluded.

Large for gestational age (LGA) defined as neonatal birth weight above the 90th percentile for gestational age and gender were determined according to the published Israeli birth weight standard(12). Macrosomia was defined as birth weight more than 4000grams. Gestational diabetes mellitus was diagnosed when abnormal glucose challenge test (140mg/dL or more) was followed by two or more abnormal values on a 3-hour (100 g) glucose tolerance test using the Carpenter and Coustan criteria(6). GDM was also diagnosed with a GCT value of 200mg/dL or higher.

The main outcomes were the development of GDM, LGA and/or macrosomia and primary cesarean delivery. Secondary outcomes were premature delivery before 37 weeks of gestation and admission for neonatal intensive care unit. We also analyzed the correlation between first trimester fasting glucose level and that of GCT and OGTT.

Fasting glucose levels were analyzed in 7 categories (<75, 75-79, 80-84, 85-89, 90-94, 95-99 and 100-105mg/dL), similar to the HAPO study(2). Data were tested for normal distribution (Kolmogorov-Smirnov test), Pearson's correlation test and multivariate logistic regression analysis were conducted in SigmaStat version 2.03 and Minitab version 12.23; Statistical significance was set at P<0.05.

RESULTS

Of the 14,550 singleton deliveries at more than 24 weeks of gestation, 7,126 women were enrollees of Clalit Health Care Services. 145 (2.0%) were excluded because they had pregestational diabetes mellitus or a first trimester fasting glucose level of 105mg/dL or more. 852 (12%) were excluded because they had a recorded fasting glucose level after the first trimester or prior to pregnancy. Among the 852 women who didn’t have a first trimester fasting glucose level and those who had it, the median maternal age was 28.7 versus 29.3 years, neonatal weight was 3269 versus 3246 grams and the rate of LGA and/or macrosomia was 10.8% versus 10.3% respectively.

The characteristics of the mothers, newborns and pregnancy outcomes are summarized in Table 1. The median fasting glucose level was 79mg/dL at a median of 9.5 weeks of gestation. More than 95% of women had a GCT done at a median gestational age
of 24.8 weeks; 781 women had a confirmatory 100gr OGT at a median gestational age of 26.7 weeks. 634 or 10.3% of neonates were LGA and/or macrosomic and 173 (2.8%) of women developed GDM. 5679 women didn't have a prior cesarean section, 843 (14.8%) of whom had a primary cesarean delivery. 436 deliveries occurred prior to 37 weeks gestation and 317 neonates were admitted to the neonatal intensive care unit.

The frequency of each primary outcome across the seven glucose categories is shown in Figure 1. With increasing fasting maternal glucose levels, the frequency of GDM development increased from 1.0% in the lowest category to 11.7% in the highest; the frequency of LGA and/or macrosomia increased from 7.9% to 19.4%, and for primary CS it increased from 12.7% to 20.0%.

Table 2 shows the associations of maternal fasting glucose as a categorical variable with each primary outcome, including adjusted odds ratios (AOR) and 95% confidence intervals (CI) for each category, as compared with the lowest glucose category. There was strong association between the development of gestational diabetes mellitus and first trimester maternal fasting glycemia, with the association increasing with increasing fasting glycemia category; the AOR was 11.92 (95% CI 5.39 to 26.37) for the highest category of the fasting plasma glucose.

BMI (body mass index) is a known confounding factor for GDM risk. Thus we performed a subgroup analysis including 4876 women in whom we had pregestational BMI data. After controlling for BMI, maternal age and parity, there was similar strong graded association between first trimester fasting glucose level and GDM with the association increasing with increasing fasting glycemia category; the AOR was 2.01 (95% CI 1.02 to 4.05) for fasting glucose level 80-84mg/dL and it increased to 9.49 (95% CI 3.87 to 23.26) in the highest category of fasting plasma glucose as compared with the lowest glucose category (P<0.0001).

We also found strong graded association between first trimester fasting glucose level and abnormal GCT (GCT>140mg/dL) with the association increasing with increasing fasting glycemia category; the AOR increased from 1.86 (95% CI 1.41 to 2.45) in the lowest glucose category to 6.85 (95% CI 4.08 to 11.48) in the highest category of the fasting plasma glucose (P<0.0001). 781 women had an OGTT; There was fair correlation between first trimester fasting glucose level and the fasting glucose at the time of OGTT, Pearson correlation coefficient 0.365, P<0.0001.

There were no significant associations between fasting glucose level category and either preterm delivery less than 37 weeks of gestation or neonatal intensive care unit admission (odds ratios 0.73 to 1.35 with 95% CI across 1 and p>0.1 in all fasting glucose categories for both preterm delivery and NICU admissions).

Importantly, there was no clear threshold for fasting glucose level that puts
pregnant women at a significantly increased risk for adverse pregnancy outcome.

CONCLUSIONS
Our results indicate associations between fasting first trimester maternal plasma glucose level, below those diagnostic of diabetes, and adverse pregnancy outcome including development of GDM, LGA and/or macrosomia and primary cesarean delivery. GDM risk remained almost unchanged even after controlling for pregestational BMI and the risk for LGA and/or macrosomia was maintained even after excluding women with GDM. We also found strong graded association between first trimester fasting glucose level and abnormal GCT and fair correlation between first trimester fasting glucose level and the fasting glucose at the time of OGTT.

Traditionally, GDM screen is recommended in the beginning of the third trimester in order to maximize the metabolic effects of pregnancy. However many protocols for GDM screening use a 2 step process thus leaving only a brief window for implementing therapeutic interventions designed to improve outcome. The benefits of screening for and treating gestational diabetes mellitus have been a matter of considerable debate(13). Advocates point to an association of gestational diabetes with maternal and neonatal morbidity. Critics argue that some past studies have failed to show that potential adverse outcomes are markedly improved by diagnosis and treatment. One potential explanation for past difficulty in identifying a benefit from screening for and treating GDM is that such screening as typically implemented does not occur until the third trimester, a point late in pregnancy thus allowing only a brief period for intervention. Indeed, approximately 20% of fetuses have already signs of macrosomia (abdominal circumference above the 90% percentile in ultrasound exam) at the time the women were first referred for GDM treatment(14). Several recent studies provide contemporary evidence that screening for and treating GDM is beneficial, and this evidence has bolstered the arguments of those who favor universal GDM testing(15-17). Nevertheless, outcomes found in the treatment arms of these studies as well as those observed in general clinical practice suggest that there is room for improvement even within the recommended testing paradigm. Earlier detection of women at risk for GDM might allow earlier intervention, in order to reduce either the later diagnosis of GDM or its associated morbidities. For example, first trimester testing and identification of high risk women allows proper diet and exercise guidance from the beginning of the second trimester. At a time when the vomiting period ends and usually the women's appetite is greatly increased. Such guidance from early pregnancy might reduce the rate of excessive weight gain that greatly increase the risk of pregnancy complications including macrosomia, cesarean section, shoulder dystocia etc(18-21).

GDM is similar to type 2 diabetes in many aspects including treatment. It is well documented that we can prevent or delay the development of type 2 diabetes in nonpregnant population at risk for type 2 diabetes by lifestyle intervention including diet modification, weight reduction and exercise(22). It is thus possible that earlier recognition of women at risk for the development of GDM and other adverse pregnancy outcome might benefit from earlier detection and intervention. Indeed a small study found that first trimester screening and therapy in women at high-risk for GDM results in AGA newborns(9). Another study has showed that early glucose tolerance screening could prevent some diabetes-related complications in women with gestational diabetes(7). Also, several large population studies(18-21) found that excessive weight gain during pregnancy, especially in
overweight and obese pregnant women, greatly increase their risks for adverse pregnancy outcomes including LGA infants and cesarean delivery. Whereas recreational physical activity performed before and/or during pregnancy is associated with a reduced risk of GDM(23). Physically active women are also less likely to develop pre-eclampsia and excessive gestational weight gain(24).

In the current study we found that higher first trimester fasting plasma glucose levels, below those diagnostic of diabetes, were associated with higher risk for GDM development later in pregnancy. Interestingly, a large observational study among young men have found that higher fasting plasma glucose levels, within the normoglycemic range (i.e. less then 100mg/dL), constitute an independent risk factor for the development of type 2 diabetes mellitus within a few years(25).

Our results for first trimester fasting glucose level are similar to the HAPO study; for example in the HAPO study a fasting glucose level of 90mg/dL or more was found in 11.9% of pregnant women in the beginning of the third trimester, this cutoff detected 22.1% of LGA neonates and 15.1% of primary cesarean deliveries. In the current study fasting glucose level of 90mg/dL or more was found in 11.4% of pregnant women during the first trimester, it identified 17.7% of LGA neonates, 12.2% of women who had a primary cesarean delivery and 38.1% of women who later developed GDM.

First trimester screening by fasting glucose level also offers the opportunity to detect and treat undiagnosed pregestational DM, that becomes a major problem as the prevalence of DM increases rapidly. Otherwise, these high risk women wouldn't receive any special treatment until the beginning of the third trimester. Also, unrecognized and untreated pregestational DM have increased risk for congenital malformations, intrauterine fetal deaths etc, that wouldn't get appropriate attention if the diagnosis was not made in early pregnancy.

There are several limitations to our study. Due to the retrospective nature of the study we cannot be sure that all the glucose tests were done as they should, i.e. after appropriate fasting or after the appropriate glucose challenge test. The 12% of women who didn't have a recorded fasting glucose test during the first trimester were excluded; we believe that this is unlikely to materially affect our results since the differences in maternal age, neonatal weight and LGA rate were small between those who had a first trimester fasting glucose and those who did not. GDM data is somewhat incomplete since only 95.1% of women had a GCT and 9% of women with an abnormal GCT did not have a diagnostic 100gram OGTT, however it is unlikely that this might have changed the results substantially. Our analysis was restricted to women who are insured by Clalit HMO. The Israeli National Health Insurance Law provides universal health services to every resident at the same cost. Thus it is unlikely that this had a significant bias on our results. The study was conducted in a single center and this might influence the results, mainly in regard to mode of delivery and NICU admission; however the main outcomes of the study LGA risk and the development of GDM are not influenced by hospital policy. Also, since it is a single center study, we can not be sure about the relevance of the study in other parts of the world. Some confounders, such as previous gestational diabetes mellitus or previous macrosomia, may have influenced clinical decisions such as the choice of route of delivery.

In conclusion, we found that fasting first trimester glucose level lower than what is considered impaired fasting glucose in the non pregnant state is associated with adverse pregnancy outcome. It may help identify and treat, early in pregnancy, apparently healthy women in order to improve pregnancy
outcome. A large, prospective multicenter study on maternal and neonatal outcome is needed to better evaluate the association of first trimester fasting glucose levels, and the usefulness of timely interventions on pregnancy outcome.

ACKNOWLEDGMENTS

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Disclosure: All authors state that they don't have any relevant conflict of interest.

FIGURE 1. The Relationship between Maternal First Trimester Fasting Glucose Level and Frequency of Primary Outcomes.
REFERENCES


Figure 1

GLUCOSE CATEGORY
Fasting glucose categories are defined as follows: category 1, less than 75mg/dL; category 2, 75-79mg/dL; category 3, 80-84mg/dL; category 4, 85-89mg/dL; Category 5, 90-94mg/dL; category 6, 95-99mg/dL and category 7, 100-105mg/dL.

TABLE 1. Characteristics of Women, Newborns and Frequency of Outcomes

<table>
<thead>
<tr>
<th>Median (interquartile Range)</th>
<th>No. of participants (%)</th>
<th>Maternal and Neonatal Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parity</td>
<td>6096 (99.5)</td>
<td>Parity</td>
</tr>
<tr>
<td>Maternal Age (years)</td>
<td>6129 (100)</td>
<td>Maternal Age (years)</td>
</tr>
<tr>
<td>Neonatal birth weight (grams)</td>
<td>6128 (100)</td>
<td>Neonatal birth weight (grams)</td>
</tr>
<tr>
<td>Gestational age at delivery (wks)</td>
<td>6129 (100)</td>
<td>Gestational age at delivery (wks)</td>
</tr>
<tr>
<td>Gestational age at fasting glucose (wks)</td>
<td>6129 (100)</td>
<td>Gestational age at fasting glucose (wks)</td>
</tr>
<tr>
<td>Fasting glucose level (mg/dL)</td>
<td>6129 (100)</td>
<td>Fasting glucose level (mg/dL)</td>
</tr>
<tr>
<td>Glucose challenge test (mg/dL)</td>
<td>5827 (95.1)</td>
<td>Glucose challenge test (mg/dL)</td>
</tr>
</tbody>
</table>

% No. with outcome Maternal and Neonatal Outcomes

| 10.3 | 634 | LGA and or Macrosomia |
| 2.8  | 173 | Gestational Diabetes Mellitus |
| 14.8 | 843 | Primary Cesarean delivery* |
| 7.1  | 436 | Preterm delivery < 37weeks |
| 5.2  | 317 | NICU admission |

*There were 5679 women without previous CS
TABLE 2. Adjusted Odds Ratios for Associations between Maternal Glucose as a Categorical Variable and Primary Outcomes.*

<table>
<thead>
<tr>
<th>FAST GLU</th>
<th>Number of total (%)</th>
<th>No. GDM (% with outcome)</th>
<th>GDM OR (C.I)</th>
<th>LGA and/or Macrosomia (% outcome)</th>
<th>LGA and/or Macrosomia OR (C.I)</th>
<th>No. 1st CS (% with outcome)</th>
<th>1st CS OR (C.I)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;75</td>
<td>1525 (24.9)</td>
<td>15 (1.0)</td>
<td>1.0</td>
<td>120 (7.9)</td>
<td>182 (12.7)</td>
<td>1.0</td>
</tr>
<tr>
<td>2</td>
<td>75-79</td>
<td>1587 (25.9)</td>
<td>31 (2.0)</td>
<td>1.95 (1.05-3.62)</td>
<td>134 (8.4)</td>
<td>222 (14.9)</td>
<td>1.08 (0.84-1.40)</td>
</tr>
<tr>
<td>3</td>
<td>80-84</td>
<td>1427 (23.3)</td>
<td>34 (2.4)</td>
<td>2.39 (1.30-4.42)</td>
<td>168 (11.8)</td>
<td>195 (14.8)</td>
<td>1.56 (1.22-2.00)</td>
</tr>
<tr>
<td>4</td>
<td>85-89</td>
<td>893 (14.6)</td>
<td>27 (3.0)</td>
<td>3.04 (1.60-5.75)</td>
<td>100 (11.2)</td>
<td>141 (17.0)</td>
<td>1.48 (1.12-1.95)</td>
</tr>
<tr>
<td>5</td>
<td>90-94</td>
<td>415 (6.8)</td>
<td>39 (9.4)</td>
<td>9.32 (5.07-17.14)</td>
<td>61 (14.7)</td>
<td>58 (15.9)</td>
<td>2.02 (1.45-2.80)</td>
</tr>
<tr>
<td>6</td>
<td>95-99</td>
<td>179 (2.9)</td>
<td>15 (8.4)</td>
<td>8.63 (4.13-18.04)</td>
<td>31 (17.3)</td>
<td>28 (17.3)</td>
<td>2.45 (1.60-3.77)</td>
</tr>
<tr>
<td>7</td>
<td>100-105</td>
<td>103 (1.7)</td>
<td>12 (11.7)</td>
<td>11.92 (5.39-26.37)</td>
<td>20 (19.4)</td>
<td>17 (20.0)</td>
<td>2.82 (1.67-4.76)</td>
</tr>
</tbody>
</table>

* Associations were adjusted for parity and maternal age.
† Data for women who had a previous cesarean section were excluded.