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Adverse Neonatal and Maternal Outcomes Associated With Impaired Glucose Tolerance Below the Threshold for Diagnosis of Gestational Diabetes [Version 1, 1 Approved, 1 Approved with Reservation]

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Abstract

Objectives: The goal of this study is to determine the maternal and perinatal risks associated with impaired glucose tolerance (IGT) below the threshold for diagnosis of gestational diabetes (GDM).

Methods: This was a retrospective chart review of 235 patients who underwent screening for gestational diabetes at 24-28 weeks' gestation. We identified 121 patients as having IGT, defined as failure of the screening 1-hour glucose challenge test (GCT), but going on to pass the diagnostic 3-hour oral glucose tolerance test (OGTT) with either zero or one abnormal value. We also identified two control groups of patients, one with normal glucose tolerance (NGT) defined as passing the screening 1-hour GCT, and a second with overt GDM, define as failure of the 3-hour OGTT with at least two abnormal values. Outcomes included large-for-gestational-age (LGA), primary cesarean section rate, development of preeclampsia or gestational hypertension, NICU admission and neonatal hypoglycemia. Chi-squared and Z-test was preformed to determine statistical significance.

Results: Our results demonstrate a statistically significant increase risk of preeclampsia ($P<0.01$, $z=3.02$), LGA ($P<0.05$, $z=2.36$) and primary cesarean section rate ($P<0.01$, $z=2.97$) in mothers with IGT compared to mothers with NGT. Additionally, we observed an increase in NICU admission (11.6% vs 3.4%), neonatal hypoglycemia (4.1% vs 0%) and gHTN (13.2 vs 5.1%), in women with IGT compared with NGT, although these results were not statistically significant. We found no statistically significant difference in preeclampsia, LGA, primary cesarean section rate, NICU admissions, neonatal hypoglycemia, and gestation hypertension when comparing women with IGT with GDM.

Conclusion: There is an increased risk of LGA, primary cesarean section, preeclampsia, gestational hypertension, NICU admission and neonatal hypoglycemia associated with IGT below the threshold for diagnosis of GDM.

Keywords

Gestational Diabetes; Impaired Glucose Tolerance; Preeclampsia; Large for Gestational Age

Introduction

Gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance with onset or first detection during pregnancy. Diabetes mellitus (DM) is estimated to effect up to 6-7% of all pregnancies, equivalent to more than 250,000 cases annually [1-3]. GDM accounts for 90% of all cases of DM in pregnancy [3,4]. GDM has consistently been linked to adverse maternal and neonatal outcomes including the development of gestational hypertension, preeclampsia, cesarean delivery, macrosomia, neonatal hypoglycemia, shoulder dystocia, birth trauma, hyperbilirubinemia, and stillbirth [3-5].

Throughout most of the world the diagnosis of GDM is established using a 1-step, 75g oral glucose tolerance (OGTT) which is endorsed by the International Association of Diabetes in Pregnancy Study Group (IADPSG) (Table 1). However, in the United States, diagnosis of GDM is most commonly established by a two-step approach. All pregnant women undergo screening with a 1-hour, 50g glucose challenge test (GCT). Women with an abnormal GCT go on to take the 3-hour, 100g OGTT. Based on research conducted in the 1960s, diagnosis of GDM is made with 2 abnormal values on the OGTT with the use of either the Carpenter and Coustan or National Diabetes Data Group cut-offs [3,6; Table 2].

Table 1: Threshold Values for the Diagnosis of GDM in Pregnancy based on International Association of Diabetes and Pregnancy Study Groups (IADPSG). This is based on 75g OGTT. One or more value must be equal to or exceed these values for diagnosis of GDM.
Adapted from International Association of Diabetes and Pregnancy Study Groups Consensus Panel: Recommendations on the diagnosis and classification of hyperglycemia in pregnancy, Diabetes Care 33: 676-682

Plasma Glucose Measurement	**Plasma Glucose Concentration** (mg/dL)
Fasting	92
1-hour	180
2-hour	153

Table 2: Diagnostic Criteria for Gestational Diabetes. Based on 2-step method utilizing 3-hour OGTT. Proposed cut-offs based on the Carpenter and Coustan vs National Diabetes Data Group criterion. Two abnormal values are needed to establish diagnosis of GDM. Adapted from American College of Obstetricians and Gynecologists: Gestational diabetes mellitus. Practice Bulletin No. 137, Obstet Gynecol 122: 406-416, 2013.

	Carpenter and Coustan Criterion Plasma Glucose Level (mg/dL)	**National Diabetes Data Group Criterion** Plasma Glucose Level (mg/dL)
Fasting	95	105
1-hour	180	190
2-hour	155	165
3-hour	140	145

Although there is a clear association between increased maternal and fetal morbidity with GDM, controversy exists regarding the risk associated with a single abnormal value on the OGTT. These patients exhibit impaired glucose tolerance, without being labeled as overt gestational diabetics. The significance of impaired glucose tolerance in pregnancy has been the subject of investigation for over 3 decades with conflicting results. Although some studies have correlated an increased risk of cesarean delivery, preeclampsia and large-for-gestational-age (LGA) with impaired glucose tolerance [7-11], other studies have contradicted these results and found no adverse associations [12,13].

Materials and Methods

This is a retrospective chart review performed at our institution with internal review board approval. Chart review was performed from February 2015 to June 2016. We included women with singleton gestation who underwent screening for GDM with 1-hour GCT at 24-28 weeks' gestation. We excluded women with extremely elevated 1-hour GCT values (>200mg/dL), because the majority of these women went on to be treated as GDM. We identified 121 patients with impaired glucose tolerance (IGT), defined as failing the GCT, but going on to pass the OGTT. This included women with no abnormal values on the OGTT and women with a single isolated abnormal value on the OGTT. We included a control group of patients with normal glucose tolerance (NGT), defined as passing the initial screening GCT. At our institution, we employ a 1-hour value less than 130 mg/dL as the threshold for passing the GCT. This group included 59 patient selected at random, age and race were not significantly different between the IGT and NGT groups. We included a second control group with GDM. This included 55 randomly selected patients with GDM, again this group shared similar age and race demographics compared to the NGT and IGT groups (Figure 1).

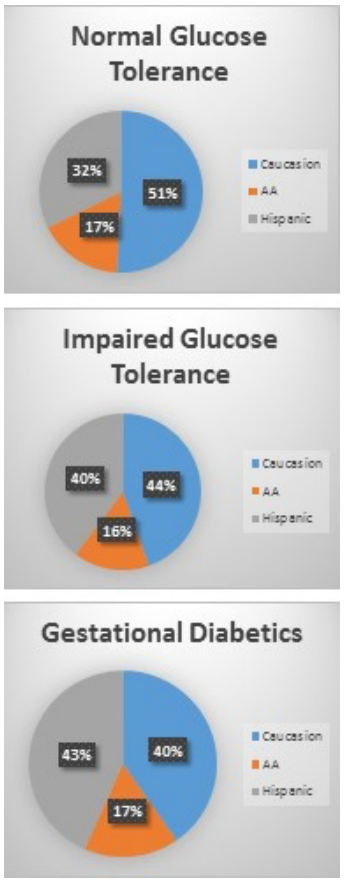

Figure 1: Study population demographics. Our patient population consisted of primarily of Caucasian and Hispanic women. The NGT group demonstrated slightly higher percentage of Caucasian patients compared to the IGT and GDM groups. The IGT and GDM groups consisted of a slightly greater percentage of Hispanic women.

First patients were identified and classified based on glucose tolerance; NGT, IGT or GDM. Patient demographics including age, race and body-mass-index were collected to ensure similar population statistics between study and control groups to minimize sample bias. Charts were then reviewed for mode of delivery, development of preeclampsia, development of gestational hypertension (gHTN), LGA, small-for-gestational-age (SGA), neonatal hypoglycemia and neonatal-intensive-care-unit (NICU) admission. LGA was defined as weight greater than the 90th percentile for gestational age. SGA was defined as weight less than the 10th percentile for gestational age. Chi-squared analysis and Z-test were used to analyze data and determine statistical significance. We utilized a P-value of <0.05 to determine statistical significance.

Results

Our results demonstrate a statistically significant increase risk of preeclampsia (P<0.01, z=3.02), LGA (P<0.05, z=2.36) and primary cesarean section rate (P<0.01, z=2.97) in mothers with IGT compared to mothers with NGT (Table 3). Additionally, we observed an increase in NICU admission (11.6% vs 3.4%), neonatal hypoglycemia (4.1% vs 0%) and gHTN (13.2 vs 5.1%), in women with IGT compared with NGT, although these results were not statistically significant (Figure 2). We found no statistically significant difference in preeclampsia, LGA, primary cesarean section rate, NICU admissions, neonatal hypoglycemia, and gestation hypertension when comparing women with IGT with GDM. Despite these results, in women with IGT compared with GDM, we did observe an overall increase in the rate of preeclampsia (17.5% vs 14.5%), primary cesarean section (38.8% vs 34.5%), LGA (18.2% vs 10.9%) and neonatal hypoglycemia (4.1% vs 3.6%). In women with GDM compared with IGT, we found and increase in NICU admissions (12.7% vs 11.6%) and gHTN (16.3% vs 13.2%).

Table 3: Results. Statistically significant increase incidences of preeclampsia, primary cesarean section and LGA in patients with IGT compared to those with NGT. IGT: Impaired glucose tolerance; NGT: Normal glucose tolerance; LGA: Large-for-gestational-age.

Condition	Percentage (%) of Patients in each group effected by condition	P-value
Preeclampsia		
NGT	1.7%	
IGT	17.4%	P < 0.01
Primary C-Section		
NGT	16.9%	
IGT	38.8%	P < 0.01
LGA		
NGT	5.1%	
IGT	18.2%	P < 0.05

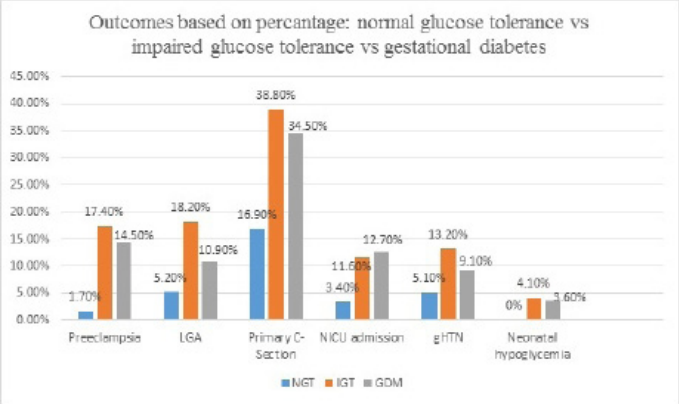

Figure 2: Outcomes based on percentage. Our results demonstrate a statistically significant increase in preeclampsia, primary cesarean section rate and large for gestational age in women with IGT compared to women with NGT. LGA: Large for gestational age. gHTN: Gestational hypertension. NGT: Normal glucose tolerance. IGT: Impaired glucose tolerance. GDM: Gestational diabetes.

Discussion

We observed an increase incidence of preeclampsia, LGA, neonatal hypoglycemia, gHTN, NICU admission and primary cesarean section rate in women with IGT compared to women with NGT. Additionally, our data shows statistically significant ($P < 0.05$) increase in preeclampsia, LGA and primary cesarean section rate. This is in agreement with multiple other studies demonstrating similar adverse outcomes [7-10]. A recent large metaanalysis by Roeckner et al. including over 4,400 patients found a significant increase in LGA, cesarean delivery, NICU admission and neonatal hypoglycemia in women with 1-abnormal OGTT value compared to women with NGT [11]. Maternal and perinatal outcomes in patients with IGT appear to be similar to those observed in women with GDM. In comparing these groups, we found no significant difference in incidence of preeclampsia, LGA, primary cesarean section, NICU admissions, neonatal hypoglycemia, gestational hypertension or SGA. This poses the question, should women with IGT be treated as GDM to improve perinatal and maternal outcomes? Several studies have investigated this question with mixed outcomes leaving us without a clear-cut answer to this question [14-16].

The Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study demonstrated a linear relationship between maternal glucose concentrations and adverse pregnancy outcomes [5]. This was a large multinational observation trial which involved over 23,000 women. Based on these findings, the IADPSG recommended new criteria for the diagnosis of GDM. These new criteria involve first trimester screening to identify overt or pregestational diabetics, as well as 1-step testing at 24-28 weeks with 75g OGTT for those women not identified as overt diabetics by first trimester screening (Table 1). Utilizing the IADPSG criteria, the overall prevalence of GDM increased to 17.8% of the pregnant population, compared to 8% to 10% with the 3-hour OGTT [17]. The new IADPSG criteria as been widely adopted across the globe and in the United States by the ADA, but controversy still exists regarding the increase number of women who will be labelled as GDM using this new criterion.

A secondary analysis of the HAPO study was conducted and found that approximately 70% of the patients diagnosed by the IADPSG criteria had only one abnormal OGTT value, or IGT [17]. These patients would be omitted from diabetic management if using the traditional 2-step testing. Supporters of the IADSPG 1-step testing argue that this method captures more women with IGT who are subject to adverse pregnancy outcomes, and should be used to establish diagnosis of GDM and guide management [18].

Preeclampsia has been associated with long-term maternal cardiovascular risks including ischemic heart disease, hypertension, stroke, venous thromboembolism and all-causes of mortality [19-22]. Preeclampsia is also associated with adverse pregnancy outcomes including preterm delivery and NICU admission [23]. GDM has been linked to the development of hypertensive disorders of pregnancy, including preeclampsia [24]. Although our results did not demonstrate a statistically significant difference in incidence of gHTN in women with IGT compared to those with NGT, the percentage of women with IGT effected by gHTN was considerable higher (13.2% vs. 5.1%). Up to half of all women with gHTN will go on to develop preeclampsia [25]. Treating women with IGT may decrease the incidence of preeclampsia, which would lead to a reduction in pregnancy associated morbidity as well as reduce cardiovascular risk later in life.

Our results demonstrated an increased risk of cesarean section and LGA in women with IGT compared to women with NGT. We suspect this increase in cesarean delivery rate is partially secondary to the large infant birth weight. There is a direct correlation between maternal glucose concentrations and neonatal birth weight. The HAPO study demonstrated a linear correlation between elevated fasting and postprandial glucose values with both birth weight and fetal adiposity [5]. The DIEP study and a study by combs et al found similar trends between macrosomia and elevated postprandial glucose levels [26,27]. Similarly, Durnwald et al and McFarland et al demonstrated that this increased cesarean section rate associated with increased shoulder and trunk adipose in macrocosmic infants of diabetic mothers [28,29]. Cesarean section is associated with greater maternal morbidity compared with vaginal delivery. Including increase in patient infection rates, hemorrhage, thromboembolism and overall mortality [30-32]. Identification and treatment of women with IGT could lead to a decrease in LGA and therefore a decrease in the cesarean section rate and the associated morbidity.

Conclusion

The key observation from our study is that women with IGT are at increased risk for adverse maternal and neonatal

outcomes. Our findings suggest that hyperglycemia is not an all-or-nothing phenomenon, but instead a linear equation, that even at lesser degrees can lead to poor maternal and neonatal outcomes. Our study, like others before it, puts into question the current diagnostic criterion for GDM, and suggests the importance of identifying women with lesser degrees of IGT. A large prospective randomized controlled trial comparing active management of women with IGT vs expectant management is needed to evaluate the benefits of treatment in this patient population.

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