PHARMACOLOGICAL TREATMENT OF GESTATIONAL DIABETES AND ASSOCIATION WITH ADVERSE MATERNAL AND NEONATAL OUTCOMES

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ABSTRACT

WENDY CAMELO CASTILLO: Pharmacological treatment of gestational diabetes and association with adverse maternal and neonatal outcomes
(Under the direction of Michele Jonsson Funk)

Background: In the United States, insulin is the only approved treatment for gestational diabetes (GDM). Glyburide has been used off-label as an alternative but there is still uncertainty regarding its safety and effectiveness in pregnancy.

Purpose: 1) To identify trends and factors associated with use of glyburide, 2) to estimate the association between glyburide and adverse maternal or neonatal outcomes.

Methods: We conducted a retrospective cohort study of commercially insured women with GDM with a pharmacy claim for glyburide or insulin 150 days prior to delivery, identified in an administrative claims database from 2000-2011. We excluded women <15 years or >50 years, with prior type 2 diabetes, or multiple gestations. We estimated trends over time in the use of glyburide versus insulin. Binomial regression was used to estimate prevalence ratios (PR) and 95% CI for the association between covariates of interest and treatment with glyburide. We used inverse probability of treatment weights to adjust for confounding and binomial regression to estimate risk ratios (RR), risk differences (RD) and their 95% confidence intervals (CI).

Results: Among 9,180 women who met inclusion criteria, 54% were treated with glyburide. From 2000-2011, glyburide use increased steeply from 8.5% to 64.5%. Women with metabolic syndrome (0.71 CI 0.50, 0.99) and hypothyroidism (0.89 CI 0.81, 0.97) were less likely to be treated with glyburide. After weighting, newborns from women treated with glyburide were at increased risk for NICU admission (1.39 CI 1.21, 1.59), respiratory distress (1.60 CI 1.21, 2.11), hypoglycemia (1.39 CI 1.00, 1.94), birth injury (1.36 CI 1.01, 1.84) and large for gestational age (1.43 CI 1.16, 1.76) compared to those treated with insulin. The absolute increase in risk in the glyburide group was 2.9% (CI 1.69, 4.00) for NICU admission, 1.4% (CI 0.60, 2.20) for large for gestational age and 1.1% (CI 0.46, 1.68) for respiratory distress.

Conclusions: Glyburide has replaced insulin as the preferred treatment for GDM over the last decade. Newborns from mothers treated with glyburide are more likely to experience adverse events. Identification of subgroups of women more likely to benefit from glyburide is a public health priority.

To my parents

To all my loved ones

To all those who believed

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"It is good to have an end to journey toward; but it is the journey that matters, in the end."— Ernest Hemingway

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LIST OF ABBREVIATIONS

95%CI	95% Confidence Intervals
AAPC	Average Annual Percent Change
ACHOIS	Australian Carbohydrate Intolerance Study in Pregnant Women
ACOG	American Congress of obstetricians and gynecologists
APC	Annual Percent Change
BMI	Body Mass Index
CPT	Current Procedural Terminology
GDM	Gestational Diabetes Mellitus
HAPO	Hyperglycemia and Perinatal Outcomes Study
ICD9	International Classification of Diseases, Ninth Revision, Clinical Modification coding
IPTW	Inverse Probability of Treatment Weights
LGA	Large for Gestational Age
LOINC®	Logical Observation Identifiers Names and Codes
MFMU	Maternal-Fetal Medicine Units Network Trial
NICE	National Institute for Health and Care Excellence
NICU	Neonatal Intensive Care Unit
NPH	Neutral Protamine Hagedorn Insulin
OGTT	Oral Glucose Tolerance Test
PCOS	Polycystic Ovarian Syndrome
PR	Prevalence Ratios
RCT	Randomized Controlled Trial
UK	United Kingdom
US	United States

CHAPTER I- REVIEW OF THE LITERATURE

1.1 Background and significance

Management of gestational diabetes mellitus (GDM) is one of the major challenges that women and their obstetricians face during pregnancy. GDM is defined as glucose intolerance first recognized during gestation (1). Approximately 2-10% of pregnant women develop the condition with variations in its prevalence depending on the population and the definition used for diagnosis. Initial management of GDM as recommended by guidelines consists of dietary counselling, self monitoring of blood glucose and exercise (2). If initial management fails to achieve glucose control then pharmacological treatment should be considered. There is debate regarding target glucose values should be achieved and there are no established guidelines for initiation of pharmacological treatment in women with GDM (3).

Two randomized controlled trials (RCTs) have examined the effect of GDM treatment (with or without medication) on women with diagnosed GDM: the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) (4) and the Maternal-Fetal Medicine Units Network trial (MFMU) (5). In both trials treatment included dietary recommendations, exercise and insulin if required, with a goal of maintaining fasting and postprandial glucose values below a defined cut point. Overall treatment proved to be beneficial in improving both maternal and neonatal

outcomes. Both studies showed a reduction of macrosomia (ACHOIS RR 0.62 95%CI 0.34,0.64; MFMU 0.49 95%CI 0.32,0.76) and preeclampsia (ACHOIS RR 0.70 95%CI 0.51, 0.95; MFMU RR 0.63 95%CI 0.42,0.96).The MFMU trial showed a reduction in the risk of shoulder dystocia (RR 0.37 95%CI 0.14, 0.97) while in the ACHOIS there seemed to be a protective effect which was not statistically significant (RR 0.46 95%CI 0.19, 1.10). Bone fracture and nerve palsy were not observed in the ACHOIS trial, while the MFMU trial did not ascertain these outcomes. None of the trials was able to assess risk of stillbirth, due to absence of outcomes. The risk of hypoglycemia, jaundice or respiratory distress syndrome did not differ between treatment groups in either trial. Approximately 8% of women in the MFMU and 20% of women in ACHOIS trial who received treatment required insulin therapy.

Although these trials provided evidence of the beneficial effects of treatment, there is lack of agreement on how early treatment should be started, when pharmacological intervention is required and which pharmacological agents should be used. There is debate regarding which therapeutic class may be more beneficial in achieving glucose control and therefore preventing adverse events.

1.2 Pharmacological treatment of GDM

Even though insulin has been the treatment of choice, some European countries and South Africa have been using oral agents for many years (6, 7). Presently insulin is the only pharmacological treatment endorsed by ACOG (1) in the US, however UK NICE guidelines from 2010 have endorsed the use of glyburide as an alternative in suitable candidates (8).

The principles for pharmacological treatment in women with GDM have been discussed by Coustan and are based on three considerations: first, whether the medication crosses the placenta; second, if crossing the placenta how it affects the fetus; and third, if adequate glucose control can be achieved in the mother and thus prevent outcomes associated with hyperglycemia (9). Although human and NPH insulin have been the treatment of choice because they do not cross the placenta, glucose control is not always easily achieved and side effects occur, the most concerning being hypoglycemia (10).

Some of the newer insulins such as the rapid acting insulins (lispro, Aspart and glulisine) and long acting insulins (detemir, glargine), can cross the placenta in animal models in a dose dependent manner (11, 12). Among women with pre-gestational diabetes and GDM, rapid acting insulins do not appear to be associated with an increased risk of adverse effects and could provide better glucose control and less hypoglycemia compared to human insulin (10). Evidence for the efficacy of insulin glargine comes from pregnant women with type 1 or 2 diabetes, where glycemic control appears to improve when compared to short acting insulins. However there is insufficient data on its safety (13, 14). There are currently no data on insulin glulisine or detemir in pregnancy.

In women with GDM, the need for multiple daily injections (2-3/day), ideal storage conditions, costs and intricacies of insulin therapy may compromise appropriate use and adherence to treatment. Given that GDM is a physiological state of insulin resistance, there has been debate on whether alternative therapies

that improve resistance would be more appropriate than insulin. In light of this, oral agents have been proposed as an alternative for women with GDM.

The debate regarding the use of oral agents in pregnancy began when they became available on the market in the 1970s. They can be classified into three groups according to their mechanism of action: insulin secretagogues (those that stimulate insulin secretion), insulin sensitizers (which modulate insulin resistance) and α-glucosidase inhibitors (which affect glucose absorption) (15). The majority of research on safety and efficacy has been conducted on glyburide and metformin.

The mechanism of action and ease of use of oral agents make them attractive for the population of pregnant women, but concerns regarding teratogenicity and potential for neonatal hypoglycemia have always been present. This was especially true for the first generation sulphonylureas which proved to be teratogenic in animal models (16). On the other hand, second generation drugs such as glyburide and metformin have a different profile. In Table 1 the drug classes, mechanism of action and evidence on safety of oral agents is presented. We will focus our discussion on glyburide and metformin since they are the two oral medications most commonly used for women with GDM.

Glyburide

The study by Langer in 2000 (17) was the first RCT to compare glyburide to insulin in women with GDM. Since then, two more RCTs (18, 19), several observational studies (20-22) and meta-analyses (8, 23) have compared the safety or effectiveness of the two drugs. In the studies reported in the meta-analysis by the

National Screening Committee, only five of the studies looked at congenital malformations: one had no outcomes in the insulin group, one found a lower risk in the glyburide group and in two the estimate was above the null for those on glyburide, although not statistically significant (8). Among those studies there is no agreement on which drug may be associated with a lower risk for maternal hypoglycemia, preeclampsia, macrosomia, and respiratory distress. There appears to be a higher risk of jaundice, neonatal hypoglycemia, and birth trauma associated with the use of glyburide although confidence intervals include the null. In both RCT's and observational studies NICU stay was lower among those treated with glyburide. A limitation of all these studies was their sample size, with the largest study having only ~250 women per group, yielding imprecise estimates (24). None of the trials ascertained obstetric trauma in the mother.

Metformin

Due to its mechanism of action, metformin appears to be an ideal choice for the treatment of GDM. Animal and experimental models have shown that metformin does cross the placenta and thus concerns about its effect on fetal metabolism have limited its use in pregnancy. Before 2008, a few small studies had compared the safety and efficacy metformin versus insulin in women with GDM. In the studies reported in the meta-analysis by the National Screening Committee, only one RCT and two observational studies ascertained congenital malformations; outcomes were observed only in two studies where there seemed to be a protective effect of metformin (8).

1.3 Adverse maternal and neonatal outcomes in women with GDM

Overall, the goal of treatment whether pharmacological or not is to achieve glucose control. Previous studies like the Hyperglycemia and Perinatal Outcomes Study (HAPO) have showen that in women with elevated fasting and 1h, 2h or 3h glucose values, the risk of adverse outcomes increases proportionally to increasing glucose levels (25). Therefore higher glucose values at baseline may put women at elevated risks, independent of successful glucose control. However for some outcomes other risk factors, such as obesity, could directly affect outcome by modifying glucose control. In this section we will discuss the role of glucose control and other relevant factors in the risk of adverse maternal/neonatal outcomes in women who initiate pharmacological treatment.

1.3.1 Maternal Outcomes

Severe perineal trauma is defined as 3rd-4th degree perineal tears occurring during delivery. Third-degree tears are defined as a partial or complete disruption of the anal sphincter muscles, where fourth-degree tears involve the rectal mucosa (26). In women with severe perineal trauma, the risk of subsequent fecal incontinence is estimated to be up to 44% (27). Risk factors associated with trauma are assisted vaginal delivery, macrosomia and age (28, 29).

1.3.2 Neonatal Outcomes

During pregnancy, the most important factors that regulate glucose availability and insulin secretion in the fetus are maternal glucose control and placental function. The fetal pancreas begins insulin secretion as early as week 8-10 of development.

Secretion peaks during the last trimester and plays a critical role in fetal growth (30, 31). In a normal pregnancy, glucose transport across the placental barrier will be equivalent to fetal demand (32). In GDM pregnancies, since glucose diffuses across the placental barrier by concentration gradient, glucose availability exceeds fetal demand, leading to increased secretion of insulin from the fetal pancreas. Depending on the level of hyperglycemia, this may lead to varying degrees of macrosomia, respiratory distress syndrome, polycythemia, or neonatal jaundice (33). At delivery, the persistence of increased insulin secretion in the neonate may put the neonate at risk for hypoglycemia (34).

Macrosomia - Large for Gestational Age: These two terms refer to the newborns weight at birth but differ in their definition. Large for Gestational Age (LGA) is defined by neonatal birthweight above the 90th percentile (usually when weight is > 4000g, but may not be always the case) in a full term infant (35). By definition, up to 10% of newborns will be LGA. The diagnosis is made after delivery as current ultrasonographic methods are inaccurate for assessment of fetal size before birth (36). Macrosomia, refers to growth beyond a threshold which usually is between 4000g- 4500g (37). Therefore while LGA uses as referent the distribution of birth weight on a given population, the cutoff for macrosomia is somewhat arbitrary. Regardless of the definition used, overgrowth in the neonate is associated with uncontrolled diabetes in pregnancy (pre-pregnancy or GDM)(25, 38), maternal obesity (39), high maternal weight gain during pregnancy, post-dates pregnancy (gestational age >41 wk), and a previous macrosomic newborn (37). Among women with diabetes in pregnancy, overgrowth can be prevented through adequate glucose

control. Besides the decreasing the risk of adverse outcomes associated with delivery, prevention of overgrowth may also prevent early delivery, cesarean section in the mother, and long term outcomes in the neonate such as metabolic syndrome and obesity (35).

Metabolic –Hypoglycemia : Among the adverse neonatal outcomes associated with diabetes in pregnancy, the definition of neonatal hypoglycemia is still controversial. It can be defined by detection of low glucose values without associated symptoms (biochemical hypoglycemia <40 mg/dL), or by clinical manifestations (clinical hypoglycemia) (41). Additionally there is currently no consensus on the levels of hypoglycemia that are predictive of neonatal injury or the glucose threshold at which treatment should be started (34). Maternal and neonatal risk factors for hypoglycemia include preeclampsia, hypertension, diabetes, preterm birth, perinatal hypoxia/ischemia, fetal growth restriction and macrosomia (40). Medications used to attain glucose control during pregnancy can have effects on the fetus, either by affecting insulin secretion in the fetus (insulin or sulfonylureas) or by limiting glucose availability (metformin).

Metabolic – Jaundice: Neonatal jaundice is defined as a yellowish tone of the skin secondary to elevated bilirubin in blood. The majority of bilirubin in serum is secondary to a turnover of red blood cells and degradation of hemoglobin. In neonates bilirubin levels are increased between the first 24-72h resolving in 1-2 weeks, also known as physiological hyperbilirrubinemia, and is secondary to a higher red blood cell turnover and reduced hepatic clearance (41). However some newborns may experience an earlier or more sustained increase that can be caused

by pathological conditions or exaggeration of the normal ones. Particularly in women with diabetes, increased production of red blood cells in the newborn (polycythemia) may place them at risk for jaundice (42). Severe hyperbilirubinemia is associated with an increased risk for bilirubin induced neurologic dysfunction, which can cause severe long term impairment at the neurological level (43). Currently it is not known how glyburide (which is metabolized in the liver), and metformin (which appears to accumulate in red blood cells) may affect the metabolism of bilirubin in fetuses of women treated with these medications.

Respiratory distress syndrome: Regardless of gestational age, respiratory failure in the neonate is a major cause of short and long-term morbidity and mortality, with its incidence decreasing with increasing gestational age (44). It is estimated that it could represent 30% of all admissions to neonatal intensive care unit (NICU) (45). Major risk factors are preterm delivery, diabetes during pregnancy, planned cesarean delivery and male gender. Vignoles et al examined the association between gestational diabetes and respiratory failure in neonates older than 34 weeks (46). After adjusting for late preterm birth, fetal growth restriction, gender and cesarean section, newborns from GDM mothers had a higher risk of respiratory failure (11.5 CI 95% 3.9-33.9). Although these findings have been described in infants born to mothers with type 1 or 2 diabetes, their incidence is less clear in women with GDM. Additionally different conditions may cause respiratory distress in the newborn (transient tachypnea, respiratory distress syndrome, meconium aspiration syndrome) (47).

Shoulder dystocia/birth injury: Both US and UK guidelines define shoulder dystocia as: ‘‘birth requiring additional obstetric maneuvers when gentle downward traction has failed to affect the delivery of the shoulders” (48). It is considered an obstetrical emergency with the potential to cause injury to the neonate and mother. The overall incidence of shoulder dystocia varies based on fetal weight, occurring in 0.6 to 1.4% of infants with birth weight between 2,500g to 4,000g, increasing to a rate of 5 to 9% among those weighing 4,000 to 4,500g, born to mothers without diabetes (49, 50).

Several factors have been associated with an increased risk for shoulder dystocia including gestational diabetes, obesity and previous shoulder dystocia a(51-53). In diabetic mothers Langer et al showed that the rate of shoulder dystocia increased three-fold when the newborn weighs more than 4500g (51). Nevertheless it is largely unpredictable. Complications from shoulder dystocia affect both the mother and newborn. The most common maternal complications are postpartum hemorrhage and fourth-degree lacerations. In the infants the most common complication are neurological and orthopedic injury, specially brachial plexus injury. Tight control of glucose levels in pregnant women with diabetes may reduce the incidence of fetal macrosomia and shoulder dystocia (25).

1.4 Summary

In women with GDM in which achievement of glucose control cannot be attained through diet therapy and physical activity, pharmacological treatment is needed. Choices of pharmacological treatment are limited due to concerns regarding

potential placental transfer and effects on the fetus. Of all available drug classes, insulin is considered to be safest and it is the only medication approved by ACOG. However in recent years randomized controlled clinical trials have provided limited evidence on the safety of glyburide during pregnancy which has led to a widespread use in clinical practice. Because women with GDM and their newborns are at an increased risk of adverse outcomes, appropriate safe and effective therapy is key during pregnancy.

Table 1. Characteristics of oral agents used for treatment of GDM

Class	Drug	Mec of Action	Benefits	Placental transfer	Effect on the mother	Effects on the fetus	References
Sulfonylureas	**Glyburide**		Improve post-prandial insulin secretion, best in patients with normal-increased weight.	Minimal		Indirect, due to glucose control	(16, 17)
Insulin sensitzers	**Metformin (Biguanides)**	Enhance insulin action, stimulating liver and peripheral uptake, suppressing liver glucose production	Reduce insulin resistance, don't cause hyperglycemia. Used for PCOS*.	Crosses barrier, fetal can be half of maternal concentrations.		Unknown	(54, 55)
	TZD†	Agonists of PPAR-γ‡ receptor, found in target tissues for insulin action	Reduce insulin resistance, don't cause hyperglycemia. Used for PCOS*.	Crosses barrier at 10 wk of gestation, fetal can be half of maternal concentrations.	Weight gain, fluid retention with edema	Unknown	(56, 57)
α-Glucosidase Inhibitors	**Acarbose**	Slow the absorption of sugars in GI ‖ tract	Decreases post meal peak	Minimal absorption in GI† tract, placental transfer unknown	Flatulence, GI† discomfort	Indirect, due to glucose control	(57)

†TZD- Thiazolidindiones; ‡ PPAR-γ- Peroxisome proliferator-activated receptor gamma *PCOS- Polycystic Ovarian Syndrome; ‖ GI – Gastrointestinal

CHAPTER II-STATEMENT OF SPECIFIC AIMS

2.1 Specific Aims

Although glyburide is used as an alternative to insulin for women with GDM there is still insufficient evidence to support its use in pregnancy. Additionally, factors such as age, maternal comorbidities, and patient preference influence the choice of drug class used for treatment but the role of these factors is unknown. With this project our objectives are to identify the factors that drive choice of initial medication among women with GDM who require pharmacological treatment, and to understand how exposure to glyburide may affect the risk of adverse outcomes in both the mother and the newborn.

In light of the unanswered questions regarding the comparative safety and effectiveness of glyburide relative to insulin, we propose to address the following aims:

2.1a Specific Aim 1

Aim: To characterize pharmacological treatment of women with gestational diabetes.

2.1a1. Describe change in trends of use of oral agents and insulin therapies in women with gestational diabetes, from 2000-2011.

2.1a2. Identify predictors of treatment and describe treatment patterns during pregnancy among gestational diabetics.

2.1a3. Describe blood glucose levels at time of diagnosis and their association with initiation and choice of treatment.

Data for this analysis came from a cohort of women with GDM identified in the Truven MarketScan® Research Databases and Truven MarketScan® Lab Databases between January 1st, 2000 and December 31st, 2011.

2.1b Specific Aim 2

Aim: Estimate comparative safety and effectiveness of oral agents versus insulin on measures of adverse maternal and neonatal outcomes.

Data for this analysis came from a cohort of women with GDM identified in the Truven MarketScan® Research Databases and Truven MarketScan® Lab Databases between January 1st, 2000 and December 31st, 2011.

2.2 Hypotheses

Based on GDM management guideline recommendations, we hypothesized that the proportion of women treated with glyburide would be lower than the proportion treated with insulin from 2000-2011. Additionally we expected a lower probability of being prescribed with glyburide among women with insulin resistance, especially those with obesity. Due to the association between glucose values at baseline and severity of GDM, we hypothesized that women with higher fasting glucose values would less likely be prescribed with glyburide.

Using the results from RCTs as evidence we hypothesized that the rate of maternal and neonatal adverse events would not be different between women treated with glyburide when compared to insulin.

2.3 Rationale

With this study we seek to understand current practices in the pharmacological treatment of women with GDM. Although the use of glyburide is acknowledged by healthcare providers, little is known about the dissemination of glyburide use since the publication of the first RCT in 2000. From a public health perspective it is important to characterize current practices and to identify factors that influence choice of initial medication.

Gestational diabetes puts women at higher risk of adverse maternal and neonatal outcomes. Measures to lower the risk include using medications to achieve glucose control in selected women. Due to their mechanism of action, ease of use and cost oral agents may be an appropriate first line treatment in this population. However evidence of safety from clinical trials is imprecise and this is partly due to their limited power to assess rare outcomes. On the other hand, the results from RCTs evaluating the effectiveness of oral agents versus insulin include populations with strict diet and glucose control which may not be reflective of usual care. Results from our study reflect real world use of these medications when compared to insulin and their impact on adverse outcomes.

CHAPTER III-METHODS

3.1 Data Source and Study Population

The source of data for this project was Truven Health MarketScan® Research Databases. This database contains individual-level, de-identified, healthcare claims information from employees, spouses and dependents who are covered by employer sponsored private health insurance. It is one of the largest collections of employer and health plan based patient data in the U.S., with approximately 30 million lives annually from January 1st, 2000 to December 31st, 2011 covering all United States (U.S.) census regions(58). The database includes information on inpatient and outpatient medical claims, linked to outpatient pharmacy data and person level enrollment information.

In addition to the commercial claims, we will be using the Truven Health MarketScan® Lab Database. This database captures results of laboratory tests for a subset of the covered lives (over 1 million) from 2007-2011, mainly representing those tests ordered in office-based practices. These results can be linked to the MarketScan® Research Databases. From our cohort of women with GDM diagnosis we will identify those with claims in the MarketScan® Lab Database.

3.2 Study Design

We conducted a retrospective cohort study of women with a GDM diagnosis who initiated glyburide or insulin, identified in MarketScan® Research Databases from years 2000-2011. The index date was defined as the date of the first claim for glyburide or insulin during pregnancy.

3.2.1 Identification of pregnancies

We sought to identify women who had claims for delivery through the use of ICD-9 diagnosis, procedure and CPT codes (Appendix 1). Since a woman could have had more than one delivery, we grouped delivery claims occurring consecutively and defined them as separate pregnancy episodes if the last claim from the first episode was at least 45 days before the earliest claim from the second episode. The earliest delivery claim for each episode was defined as the delivery date. To identify events that occurred during pregnancy and at time of delivery, women were required to be continuously enrolled during the year prior to and at least three months after the delivery date (Figure 1).

3.2.2 Identification of study population

Clinically GDM is diagnosed when a pregnant woman meets one of the following criteria: 1) fasting plasma glucose between 92-126 mg/dl , or 2) positive oral glucose tolerance test (OGTT) at 24-28 weeks of gestation. If a woman has fasting plasma glucose ≥126 mg/dl, or a random plasma glucose ≥ 200 mg/dl any time before or during pregnancy she is considered to have pre-gestational diabetes An OGTT is not recommended in women with this diagnosis (59). Since lab values

are not available for the full cohort we based our definition of GDM on the use of ICD9 codes.

For each pregnancy episode, we identified women who had a claim with a diagnosis code for GDM (ICD9 648.8-648.83) in the year prior to delivery. We excluded women 1) with diagnosis codes for type 1 or 2 diabetes, 2) under 15 years or over 50 years old, and 3) with diagnosis or procedure codes for pregnancy with multiple gestations. Our cohort was restricted to the first eligible GDM pregnancy for a given woman.

3.2.3 Linkage to newborns

Within the MarketScan® Databases, family members enrolled under the same plan share a common string in the identification number. Using the common string and year of birth, we probabilistically linked women in our cohort to children whose first claim occurred during the same calendar year as the maternal delivery code. To refine the linkage, we restricted the date of the potential newborn's first claim to within 30 days of the delivery date. Some global payments could include in the maternal claims, billable services from newborn care at time of delivery. By extending the date of the first newborns claim up to 30 days after delivery we intended to capture newborns whose care was billed separately from their mothers, newborns who generated claims not covered by their mothers insurance (such as critical care or special procedures), or healthy newborns whose first claim would be a well-baby visit (which would only occur after delivery). This allowed us to capture not only sicker newborns that generated claims around time of the delivery but also

healthier newborns that would usually get an identification number at their first outpatient visit. To be able to ascertain use of health services we required newborns to be continuously enrolled up to three months after delivery date.

3.2.4 Linkage to Laboratory Data

Screening (50g), Baseline (fasting), 1h and 2h glucose values (mg/dl) were identified from the MarketScan® Lab Database through the presence of specific Logical Observation Identifiers Names and Codes (LOINC®). In the analysis both 75g and 100gr glucose tolerance tests were included. Only the first occurrence for screening tests and OGTT was considered for the analysis.

3.2.5 Exposure

We identified women in our cohort with a pharmacy claim for insulin or glyburide in the 150 days prior to delivery. Women who had a claim for insulin or glyburide earlier than 150 days prior to delivery were excluded from the analysis since use of these medications in early pregnancy is more likely to suggest pre-pregnancy type 2 diabetes rather than GDM. Those initiating pharmacological treatment after delivery were not included in this study. Classification as an insulin or glyburide initiator was based on the drug class of the first pharmacy claim identified for a given woman.

3.2.6 Covariates

Covariates of interest included maternal age at time of delivery (estimated by subtracting the year of birth from year of delivery), year of delivery, and maternal

comorbidities. Based on subject matter knowledge and consultation with experts we identified conditions associated with initiation of treatment or the outcomes of interest. All conditions were defined through the use of ICD-9-CM diagnosis code, CPT code or generic drug name. Comorbidities of interest were: infertility diagnosis (ICD9 V26.8, V26.81 CPT 89252, 89268, 89281, 58310, 58311, 58321-23, 58970-76, 89250-57, 89268, 89272, 89280-81, 89290-91, 89352-54) or treatment (at least 1 claim for clomiphene, urofollitropin, follitropin, menotropin, ganirelix, cetrorelix); obesity (ICD9 278.0X, 649.1X,V77.8, V85.3x, V85.4); hypothyroidism (ICD9 244.X); hyperandrogenism (defined as an ICD9 code for alopecia [704.0X] , hirsutism [704.1] or acne [706.0, 706.1]); metabolic syndrome (ICD9 277.7); and polycystic ovarian syndrome (ICD9 256.4). Because metformin is used off label for infertility or to reduce risk of miscarriage we included history of metformin use as a covariate in the analysis. Etiologically it is not clear whether pregnancy induced hypertension and preeclampsia lead to GDM or viceversa. However both conditions are associated with adverse neonatal outcomes. To assess the role of pregnancy induced hypertension and preeclampsia, and avoid reverse causation, we identified women who initiated an antihypertensive or were hospitalized with a diagnosis code for preeclampsia (ICD9 642.40, 642.73) after initiation of pharmacotherapy. All other covariates were assessed in the time period prior to the index date (Figure 1).

We also investigated regional differences in practice patterns - specifically, whether the use of glyburide versus insulin was different among rural/urban areas. We used Rural-Urban Continuum Codes to identify metropolitan, urban and rural counties(60)

3.2.5 Outcomes

We defined maternal and neonatal outcomes as described in Table 2. These outcomes will be identified through ICD9 diagnosis, CPT and ICD9 procedure codes (Appendix 2). These codes were selected based upon previously published algorithms or guideline recommendations.

3.3 Data Analysis

3.3.1 Specific Aim 1

Distribution of covariates was described using univariate and bivariate analysis. Exploratory analysis of maternal age as a categorical and continuous variable was undertaken prior to multivariate modeling. Because our assumption was that the association between age and choice of initial therapy would be non-linear, we used fractional polynomials to account for this. We compared model fit between a predefined set of first degree fractional polynomial functions where the power of the function is set to -2, -1, -0.5, 0, 0.5, 1, 2, 3 (61). The function with the best fit was used in the multivariable model. Since fractional polynomial models are fit through maximum likelihood, the best-fitting model is selected based on which function yields the highest likelihood.

Trends in the use of glyburide and insulin between years 2000-2011 were estimated by calculating the proportion of women on a given treatment, using as denominator the total number of women treated with medication in a given year. Binomial regression was used to adjust for covariates of interest. To estimate the annual percent change (APC) of glyburide use we used log-linear regression

adjusted for age and covariates of interest. The slope is exponentiated to calculate the percent change per year. The underlying assumption is that the rates are linear on the logarithmic scale. Because trends of glyburide use could be non- constant over the 2000-2011 period we estimated average annual percent change (AAPC). AAPC summarizes the trend over a sub-period of interest and allows identification of transitions in the trend. We identified intervals in which the trend was linear and estimated the APC. The AAPC over any fixed interval is a weighted average of the slope coefficients of the APC with the weights equal to the length of each segment over the interval(62).

We used binomial regression to estimate prevalence ratios (PR) and 95% confidence intervals (CI) for the association between baseline characteristics (age, comorbidities, calendar time) and treatment with glyburide versus insulin.

To assess whether glucose levels at the time of GDM diagnosis influenced the choice of medication, we compared the distribution of screening, fasting, 1 and 2 hour post-test glucose values between treatment groups. We estimated the effect of blood glucose values at baseline on the probability of being prescribed glyburide versus insulin using binomial regression. Glucose values were modeled as continuous variables. We used multivariable regression with generalized estimation equations to account for correlation between glucose tests.

3.3.2 Specific Aim 2

We used logistic regression to calculate the probability of treatment with glyburide compared to insulin, adjusting for all covariates. The distributions were

examined to identify areas of non-overlap between treatment groups. Age and comorbidities were included in the model. To add flexibility to the model we also included squared terms for age. This propensity score was then used to create stabilized inverse probability of treatment weights (IPTW) to adjust for confounders in the risk model (63). Balance of measured confounders after estimating the propensity scores and distribution of the IPTWs was assessed.

Binomial regression with a log link was used to estimate risk ratios and risk differences. Robust variance was used to estimate 95% confidence intervals (RR 95%CI and RD 95%CI, respectively) for the association between glyburide and adverse outcomes. Risks were estimated using a weighted model adjusted for calendar year, using dummy variables, to account for changes in treatment over the 11 year period.

3.3.2.1Sensitivity Analysis

Because glyburide uptake occurred mostly between 2004-2006, we conducted sensitivity analysis to estimate the potential effect that early adopters of therapy could have on our estimates. Additionally because ICD9 codes for body mass index (BMI) were introduced after 2007, we were also interested in assessing the effect of the introduction of these codes on the ascertainment of obesity, which is a potential confounder in this setting. To assess this, we created three sub-cohorts that excluded women who: a) entered the cohort before 2004 (early adopters), b) entered before 2005 (transition period for glyburide uptake), c) entered before 2007.

Because our data lack information on BMI and we rely on the use of ICD9 codes to ascertain obesity, under ascertainment of this variable is possible. To investigate the impact of residual confounding we used the array approach developed by Schneeweiss (64). Given that this approach was developed to evaluate unmeasured confounding, we estimated the effect of glyburide and adverse outcomes that would have been observed when excluding obesity from our adjusted model. In this scenario we assessed how imbalance of obesity between glyburide and insulin groups could bias the observed estimates of association.

3.3.3 Software and approval

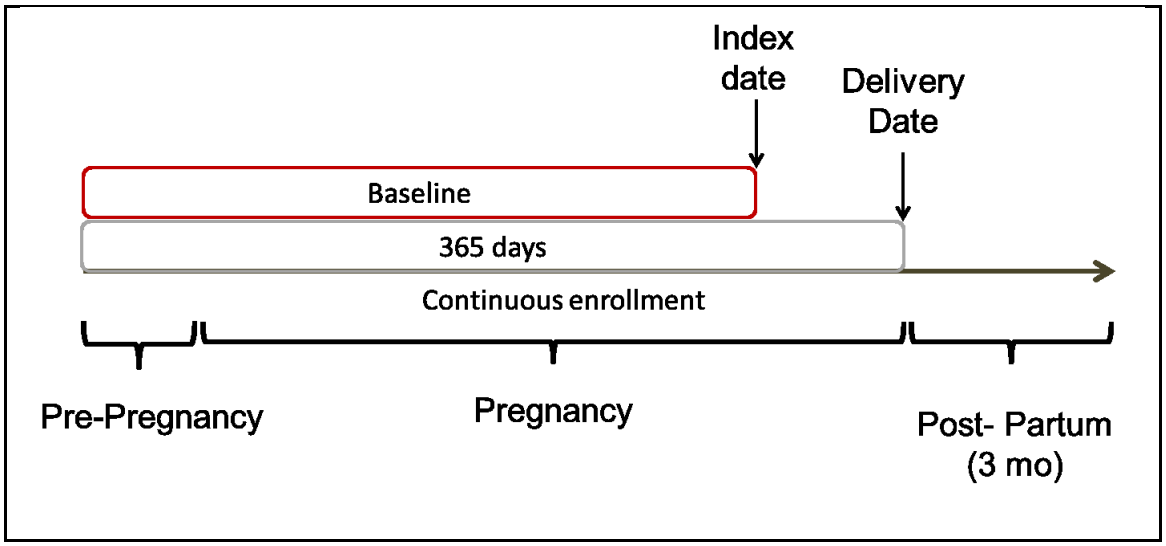
All analyses were conducted using SAS v 9.3 (SAS Institute, Cary, NC). The Institutional Review Board (IRB) at the University of North Carolina, Public Health – Nursing IRB, Office of Human Research Ethics provided approval for this study.

3.4 Tables and Figures

Table 2. Outcome definitions

	Condition	Definition	Ref
Maternal	Perineal trauma (severe)	≥1 claim with code for 3rd or 4th degree perineal laceration occurring during birth	(65)
Neonatal	NICU admission	≥1 claim with code for intensive care unit admission > 24 h	Code not validated
	Respiratory distress syndrome	≥1 claim associated with admission to NICU with ICD9 diagnosis code, excluding transient tachypnea	(66)
	Hypoglycemia	≥1 claim associated with admission to NICU with ICD9 diagnosis code for neonatal hypoglycemia.	(66)
	Jaundice	≥1 claim associated with admission to NICU with code for hyperbilirubinemia not associated to hemolytic disease. Also includes neonates with CPT or ICD9 procedure codes phototherapy or exchange transfusion.	(67)
	Shoulder dystocia/birth injury	≥1 claim with ICD9 diagnosis code for fetal disproportion, shoulder dystocia, or fetal injury (scalp, fracture)	(68)
	Preterm	≥1 neonatal claim with ICD9 code for preterm birth	(69)
	Large for Gestational Age	≥1 claim with ICD9 diagnosis code for large for gestational age	Code not validated

Figure 1. Index date and ascertainment of baseline



CHAPTER IV-GENERAL RESULTS

This chapter presents general results of this study not presented in the manuscripts. It will focus on characteristics of the cohort selection process, linkage to newborns and laboratory data, comparison of glucose distributions across treatment groups and results from the propensity score and IPTW analysis.

4.1 Cohort Selection

A flow diagram for the cohort selection process is presented in Figure 3. After applying the continuous enrollment criteria, 45% (N=1,018,383) of women with a delivery remained in the cohort. Of those, 13% were identified as having GDM and meeting inclusion criteria. Among these we identified 14,558 women with a claim for insulin or glyburide.

4.2 Linkage to newborns and laboratory data

Overall, we were able to link 82% (N=110,879) of women with GDM with a corresponding newborn (Table 3). Non linkage can be attributed to newborns being under the insurance of a father whose claims are not in the database or newborns who do not generate claims (such as stillborns). Of those with medication, 9,180 (63%) had a claim for insulin or glyburide with an index date within 150d before delivery. This final group was considered as the analytical cohort.

Laboratory data from Truven Health MarketScan® Lab Database was available for 6.1% (N=6,776) of women with GDM with linkage to a newborn (Table 3). Of the ones who initiated pharmacotherapy only 57.3% (N=359) had lab values for screening or any of the tests within the OGTT (fasting, 1hour or 2 hour tests). Reasons for missing laboratory data could be related to more billing for these services where the lab was done. Because our dataset includes claims billed by a single provider, if a woman was seen in a facility with a clinical laboratory those claims would not be captured in the database.

4.3 Comparison of distribution of glucose values between treatment groups

Figure 3 shows the distributions of the screening, fasting, one hour and two hour glucose tests for women with laboratory results in the database. Overlap between treatment groups is observed across the four tests.

4.4 Propensity Score distributions and IPTWs

Before applying the propensity score, there was evidence of imbalance in several of the covariates between the glyburide and insulin groups. In Figure 4 we observe the distribution of the propensity scores where there was considerable overlap between the two distributions, reflective of achieved balance of measured confounders. The majority of individuals had propensity scores between 0.5 and 0.6. After stabilizing IPTWs we observed a mean value of 1.0 in each treatment group with a maximum value of 1.5634 and 1.7720 in the insulin and glyburide groups respectively. No trimming was performed.

4.5 Tables and Figures

Table 3. Number and proportion of women linked to newborns and to laboratory data, 2000 - 2011

		Linkage to Newborn				Total
		Yes		No		
		N	%	No	%	
GDM	No Medication	98,605	82.1	21,533	17.9	120,138
	Medication	12,335	84.7	2,223	15.3	14,558
	Total	110,940	82.4	23,756	17.6	134,696
GDM + Lab	No medication	6,150	73.9	2,168	26.1	8,318
	Medication	626	75.3	205	24.7	831
	Total	6,776	74.1	2,373	25.9	9,149

Figure 2. Flow diagram for cohort selection

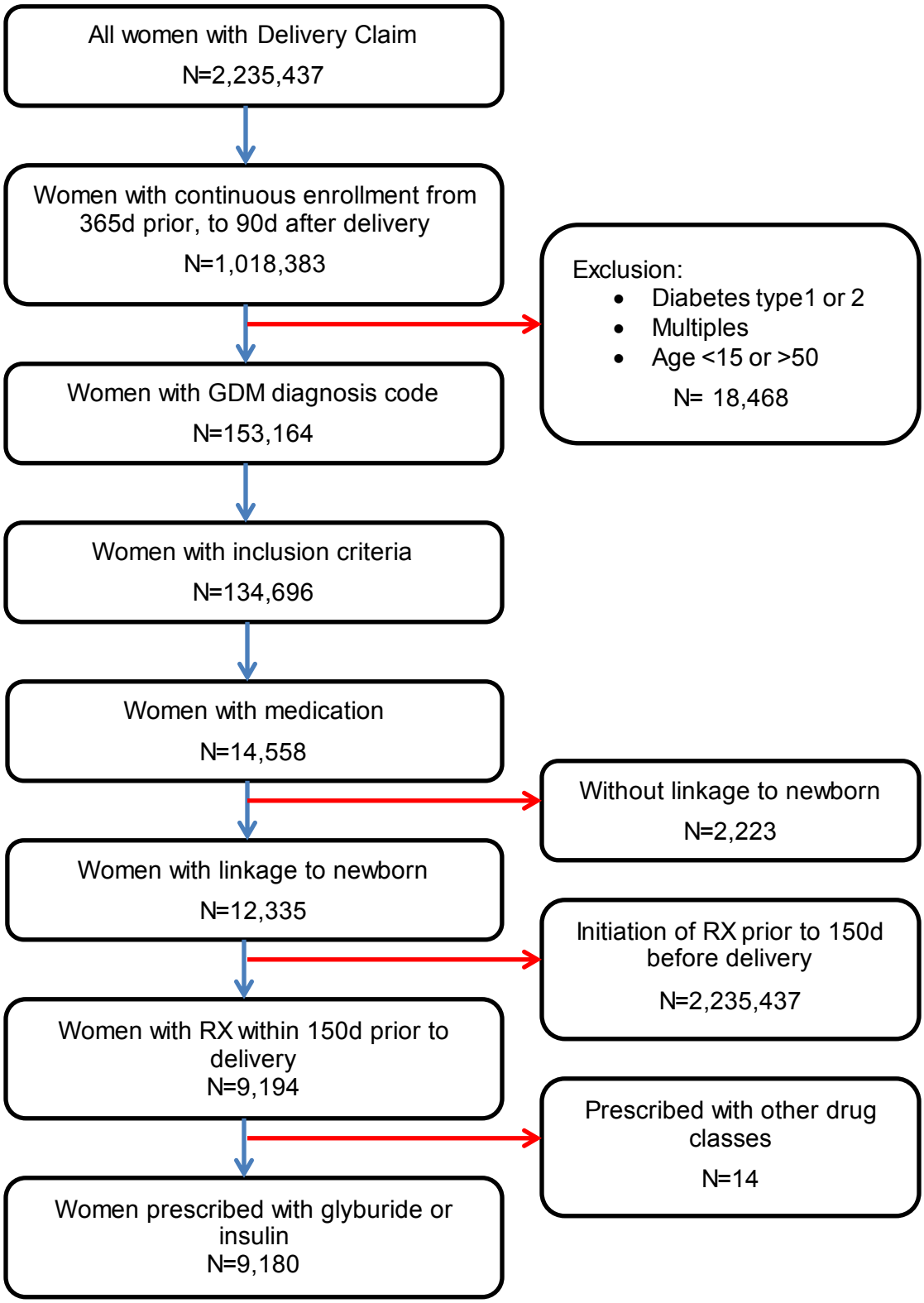
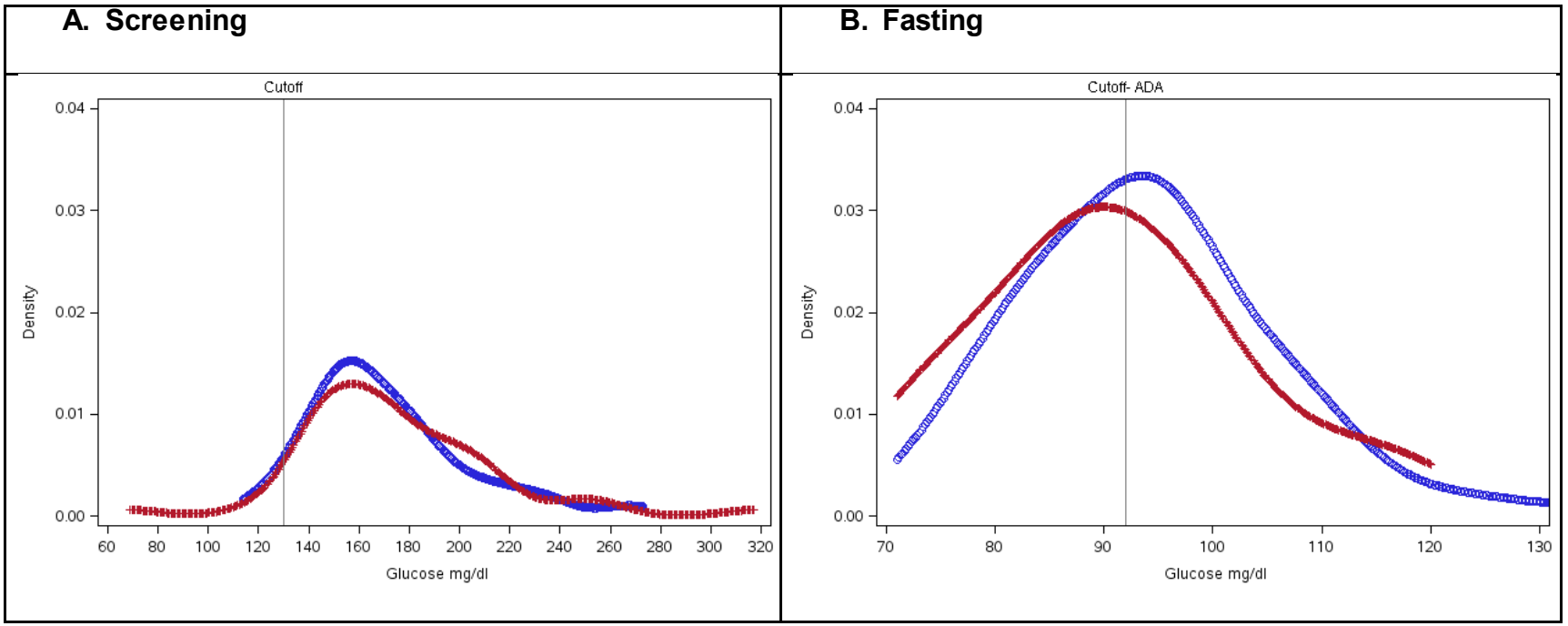
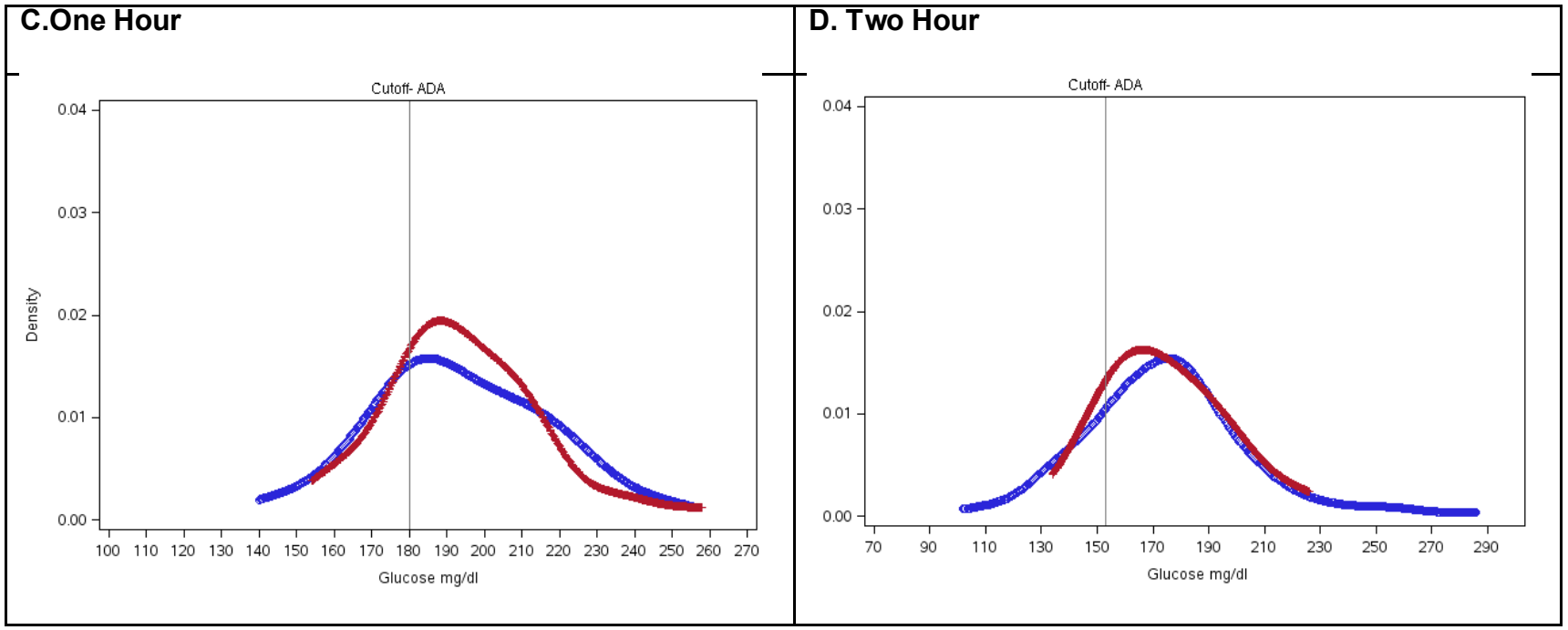


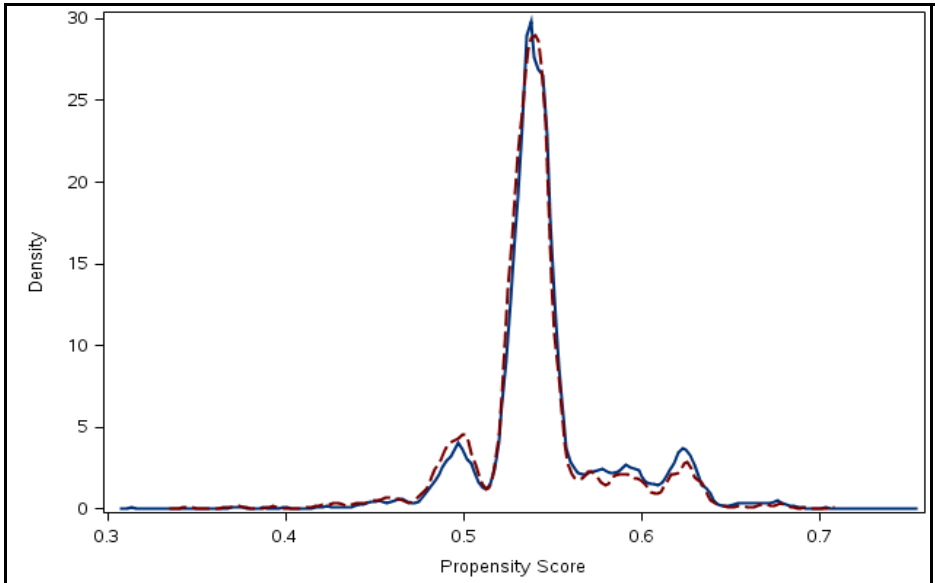
Figure 3. Comparison of distribution of glucose values for screening, fasting, one hour and two hour tests in women with laboratory data.





Distribution of glucose values from screening and OGTT at baseline. Blue- Glyburide; Red- Insulin X axis represents glucose in mg/dl, Y axis represents densities. Vertical line- American Diabetes Association (ADA) cutoff values for diagnosis of GDM.

Figure 4. Overlap between propensity score distributions of women treated with glyburide or insulin.



IPTW

	Insulin	Glyburide
Mean	1.00	1.00
SD	0.09	0.07
Max	1.56	1.77
Min	0.69	0.72
q_0	0.66	0.72
q_25	0.97	0.99
q_50	0.99	1.01
q_75	1.01	1.03
q_95	1.20	1.11
q_100	1.56	1.77

Blue- Glyburide; Red- Insulin. Right table -Characteristics of the IPTW distributions

CHAPTER V- MANUSCRIPT 1

Trends in Glyburide or Insulin Use for Treatment of Gestational Diabetes in the U.S., 2000-2011

5.1 Introduction

The prevalence of gestational diabetes mellitus (GDM) in the United States more than doubled from 1.5% in 1989-1990 to 4.2% 2001-2004, with varying prevalence rates from 5-8% across regions (70, 71). Over the last decade a substantial fraction of diagnosed women require pharmacologic treatment during pregnancy. Currently the only FDA-approved medication for the treatment of GDM is insulin (72) although glyburide (an oral agent), is also used (73).

Glyburide is a second generation sulfonylurea, thought to be effective for the treatment of GDM because this condition is characterized by an early phase of insulin resistance followed by a decrease in the pancreatic β-cell insulin response (74). Glyburide is believed to be safe because of animal and in-vitro placental studies showing minimal transfer (75, 76), although recent studies in humans have shown that umbilical cord concentrations can be 70% of those found in maternal plasma (77). Its ease of use and low cost is an additional advantage when compared to insulin which is administered by injection and entails higher costs.

In 2000, Langer et al. conducted the first randomized controlled trial (RCT) comparing glyburide to insulin in 404 women with GDM (17). Since then, two more

RCTs (18, 19), some observational studies (20, 21, 24) and meta-analyses(8, 23) have compared the safety or effectiveness of the two drugs it is unknown how evidence from these studies has affected choice of medication in routine practice and which factors influence the prescription of glyburide versus insulin.

Our objective was to characterize pharmacological treatment of women with GDM by describing trends in the use of glyburide and insulin over the last decade, and identifying predictors of treatment choice.

5.2 Results

Of 110,940 women with an eligible GDM pregnancy linked to a newborn, 9,180 (8.2%) had a pharmacy claim for insulin or glyburide during the 150 days prior to delivery (Table 4). The median age at baseline was 33 years (interquartile range 30-37). Glyburide was prescribed as the initial medication for approximately half of pregnancies overall (54.3%, N=4,986). The use of glyburide was less common in the Northeast (45.1% vs 54.9%) and slightly more common in the South (56.1% vs 44.7%) and Northcentral (55.4% vs 44.6%) regions of the US.

The use of glyburide increased steeply from 9.2% in 2000 to 64.4% in 2011. When comparing glyburide to insulin, the adjusted annual percent change was higher between 2000-2007 (31.6% 95%CI 17.8, 46.9) and reached a plateau after 2008 with an annual increase of 3.2% (95%CI 0.1, 6.5). The probability of being prescribed glyburide varied by age with a 5% decrease for every 10 year increase in age (PR 0.95, 95%CI 0.91,0.99) (Figure 5).

The proportion of women with comorbidities was generally similar between treatment groups, although those who were treated with glyburide were less likely to have a history of infertility treatment (PR 0.93, 95%CI 0.86, 1.02), PCOS (PR 0.88, 95%CI 0.78, 0.99), or hyperandrogenism (PR 0.77, 95%CI 0.62, 0.97) (Table 5). In women with obesity, there was no preference for one treatment over the other (PR 1.04 95%CI 0.98, 1.10). Women with metabolic syndrome and hypothyroidism were less likely to be treated with glyburide (PR 0.71, 95%CI:0.50, 0.99; PR 0.89 95%CI 0.83, 0.96, respectively). Prior metformin use was not associated with initiation of glyburide (PR 1.01 95%CI 0.94, 1.09).

Lab results were available from the MarketScan Lab Database® for 3.7% (N=339) of the cohort. Sixty six percent of women with lab values were in the glyburide group (N=224). When compared to the full cohort, women in the subsample were slightly older (median age 35 years, interquartile range 31-38) and obese (19.1% and 18.8% respectively for insulin and glyburide groups). Women in the insulin group had a higher prevalence of hypothyroidism (13.0%). For differences in baseline covariates for the subgroup with lab results, refer to Appendix 3. We compared the distributions of the earliest 50g screening, fasting, 1 hour and 2 hour blood glucose tests for women initially treated with glyburide or insulin. Results are presented as [mean (SD)]. Although the distributions for the two groups were similar for screening and 2 hour glucose values, the fasting values were slightly higher for those initiating glyburide [92.4 (10.9)] when compared to insulin [90.9(12.2)]. The 1 hour test results were more similar between treatment groups (glyburide [193.7(25.6)]; insulin group [192.1(24.2)]). For every 10 unit change in two-hour

glucose values, the probability of being prescribed with glyburide increased by 2% (PR= 1.02 95%CI 0.97, 1.08) (Table 6).

5.3 Discussion

We found a marked increase in the use of glyburide over the period of 2000-2011 with a corresponding decrease in insulin as first line of therapy which correlates with the publication of results from randomized clinical trials (17-19) and observational studies (20, 21, 24, 78). Our results support findings from recent studies showing widespread use of glyburide despite lack of conclusive clinical guidelines being available (79, 80).

Among the comorbidities of interest we did not find strong predictors for initiation of glyburide. Women with infertility, PCOS and hyperandrogenism were more likely to be treated with insulin as were those with hypothyroidism or metabolic syndrome. Interestingly women with an ICD9 code for obesity were equally likely to be prescribed with glyburide versus insulin. In obese women, factors other than insulin resistance, such as concerns associated with increased weight gain and distribution of insulin at injection site could be drivers of initiation of treatment with glyburide (81). Because insulin resistance is the common denominator in all these conditions, the degree of perceived insulin resistance could be an additional driver of initial choice of treatment for GDM.

In non- pregnant populations, thiazolidinediones and metformin are used to improve insulin sensitivity among individuals with type 2 diabetes. Thiazolidiendiones are contraindicated in pregnancy, and metformin crosses the

placenta and therefore its use in pregnancy is not recommended in the U.S (82). Currently metformin is used in the pre-conception period to improve insulin sensitivity among women with insulin resistance who want to conceive (83, 84). Our findings reflect this where a large proportion of women treated with metformin in early pregnancy had a diagnosis of PCOS (39% [n=205]), or were treated for infertility (26% [n=134]).

Little is known about the role of age on the preference to initiate treatment with oral agents among women with GDM. It is known that the risk for developing GDM as well as severity of the disease increases with age. In our study, 41% of women were older than 35 years which reflects the increase in the pregnancy rate among this population over the last decade (85). Among those with GDM, the probability of being prescribed glyburide decreased by 5% for every 10 year increase in age. On the other hand after the dissemination of glyburide use, younger women were more likely to be prescribed with the oral agent after 2007 (Figure 5). This provides evidence that age can be influential on the decision of which drug class to initiate.

Distributions of screening, one hour fasting and two hour glucose values at baseline were similar between the treatment groups. Glucose distributions have previously been described for treated versus untreated women with GDM, but not for women who initiated treatment (86). Although studies such as the Hyperglycemia and Adverse Outcomes in Pregnancy (HAPO) have shown that the risk of adverse maternal and neonatal outcomes is associated with increasing values of fasting

glucose at baseline, the role of these values in determining which pharmacotherapy to initiate is less certain (86).

It is important to note that there were differences between the study cohort and the sample with lab values in their baseline covariates. The sample had a higher proportion of obese and hypothyroid women, more so among those initiating insulin. After adjusting for comorbidities, two- hour glucose values could be slightly associated with type of medication. For every 10 unit increase in their fasting glucose values women were 2% more likely to be prescribed with glyburide. Fasting and one- hour values were not associated with choice of initial prescription. Glucose values before initiation of treatment may have a stronger association with choice of pharmacotherapy.

Some of the limitations of this study are absence of gestational age or information on last menstrual period, biometrics (weight or height) and race-ethnicity. Although we cannot identify the beginning of pregnancy in our cohort, we believe our definition of GDM in combination with the exclusion of women who had early pharmacy claims for the drugs of interest yields a cohort of 'true' gestational diabetics. This approach has been validated by Andrade et al where they found a PPV of 85% (95%CI 71-94%) (28). Although BMI is the gold standard to classify women as obese, we were limited to the use of ICD9 codes to identify this condition. In their study, Andrade et al validated the use of ICD9 codes for obesity and reported that positive predictive value was high (92% 95%CI 90-94) but sensitivity was low (33%) (87). This suggests that there is considerable under-reporting of obesity based on ICD-9 diagnosis codes, but, we do not expect this to be differential

between the drug classes of interest. A further limitation of ICD9 codes in this setting is the ability to identify women who are overweight, where in this subgroup preference for glyburide could be different.

Absence of race and ethnicity is a limitation of our study. Previous population based studies have shown that GDM prevalence is higher among certain racial groups such as Hispanics, Asians and Native Americans (88). Regarding initiation of pharmacotherapy, Berggren et al have reported differences were Hispanics were more likely than African Americans or Whites to receive glyburide or insulin (89). However this may not be unrelated to other factors such as access to care or low socioeconomic status among others. Since the purpose of this study is to provide an overview of glyburide use addressing racial differences is beyond the scope of this study. This cohort is representative of an insured, employed population and the results from this study may not be applicable to other populations.

Strengths of the study include sample size and ascertainment of medication use. Our cohort was selected from a large and nationally representative population of women with gestational diabetes who were pharmacologically treated over a 11 year period. When compared to previous studies only 8.3% of women with a GDM diagnosis in our study required pharmacological treatment. This contrasts with studies reporting prevalences that range between 8-43% (4, 5). However there are important differences in terms of the population due to severity of GDM, and generalizability (trials or hospital based populations). Our study likely includes women with different degrees of severity and is reflective of the full spectrum of patients treated across a range of clinical settings. By restricting our cohort to

women who were continuously enrolled in the year prior to delivery we assured that use of healthcare and pharmacy services would be observable throughout pregnancy. Therefore medication use in our study is based on pharmacy claims of dispensed drugs which allowed us to identify the earliest prescription in pregnancy. When compared to self-report, by using pharmacy claims we have better ascertainment of initiation of treatment during pregnancy.

Conclusion

Dissemination of glyburide for the pharmacological treatment of GDM has been rapid and our findings indicate that it has become the preferred choice for initial treatment, particularly among younger, non-insulin resistant women. When compared to insulin, glyburide has important advantages such as ease of use and costs, which can influence patient and provider preference (90). Since glyburide appears to have replaced insulin as the preferred treatment for GDM over the last decade, robust evaluation of glyburide's relative and effectiveness is warranted to inform treatment decisions for women with gestational diabetes. Given the short and long term implications of suboptimal glucose control in women with GDM, assessing the effectiveness of glyburide versus insulin is a clinical and public health priority.

5.4 Tables and Figures

Table 4. Characteristics of women diagnosed with GDM who initiate medication, 15-50y in a US based population, 2000-2011

	Insulin		Glyburide		
	N=4,194	%	N=4,986	%	%Δ*
Age, year- Mean(SD)	34 (4.7)		33 (4.7)		
Age, 5y categories					
15-19	4	0.1	3	0.06	-0.04
20-24	99	2.4	124	2.5	0.13
25-29	730	17.4	940	18.9	1.45
30-34	1593	38.0	1860	37.3	-0.68
35-39	1292	30.8	1508	30.2	-0.56
40-44	442	10.5	523	10.5	-0.05
>=45	34	0.8	28	0.6	-0.25
Calendar year					
2001	54	1.3	5	0.1	-1.19
2002	115	2.7	20	0.4	-2.34
2003	245	5.8	73	1.5	-4.38
2004	366	8.7	188	3.8	-4.96
2005	449	10.7	306	6.1	-4.57
2006	409	9.8	374	7.5	-2.25
2007	406	9.7	538	10.8	1.11
2008	438	10.4	661	13.3	2.81
2009	657	15.7	1003	20.1	4.45
2010	563	13.4	928	18.6	5.19
2011	492	11.7	890	17.8	6.12
Region					
Northeast	639	15.2	525	10.5	-4.71
Northcentral	1163	27.7	1442	28.9	1.19
South	1529	36.5	1955	39.2	2.75
West	838	20.0	1037	20.8	0.82
Unknown	25	0.6	27	0.5	0.05

	Insulin		Glyburide		
	N=4,194	%	N=4,986	%	%Δ*
Urbanity†					
Metro	3142	87.4	3,453	88.2	0.87
Urban	399	11.1	412	10.5	-0.57
Rural	36	1.0	39	1.0	0.00
Unknown	19	0.5	9	0.2	-0.30
Comorbidities					
Infertility treatment	283	6.7	280	5.6	-1.13
Hypothyroidism	349	8.3	353	7.1	-1.24
PCOS‡	171	4.1	162	3.2	-0.83
Hyperprolactinemia	14	0.3	11	0.2	-0.11
Hyperandrogenism	67	1.6	99	2.0	0.39
Metabolic syndrome	30	0.7	20	0.4	-0.31
Obesity	305	7.3	499	10.0	2.74
No comorbidities	3154	75.2	3773	75.7	0.47
Metformin use					
Any use before 1st Rx	283	6.7	317	6.4	-0.39

*Difference in percentage (Δ%)-Estimated by subtracting percentages in insulin column from glyburide. †Urbanity – FIPS county codes were available for women in the 2000-2010 period (Glyburide N=3,596; Insulin N=3,913). PCOS- Polycystic Ovarian Syndrome

Table 5. Association of calendar year and maternal characteristics with initiation of glyburide vs insulin. Crude vs Adjusted* Prevalence Ratios (95% Confidence Interval)

	Crude		Adjusted	
	PR	**95%CI**	**PR**	**95%CI**
Calendar year				
2001	0.13	0.06, 0.30	0.13	0.06, 0.30
2002	0.23	0.15, 0.35	0.23	0.15, 0.34
2003	0.36	0.29, 0.44	0.35	0.29, 0.44
2004	0.53	0.47, 0.60	0.52	0.46, 0.59
2005	0.63	0.57, 0.69	0.63	0.57, 0.69
2006	0.74	0.68, 0.81	0.74	0.68, 0.80
2007	0.88	0.83, 0.95	0.88	0.82, 0.94
2008	0.93	0.88, 0.99	0.93	0.88, 0.99
2009	0.94	0.89, 0.99	0.93	0.88, 0.99
2010	0.97	0.91, 1.02	0.96	0.91, 1.00
2011	1.00		1.00	
Age 10y Change (Continuous)	0.96	0.93, 1.00	0.95	0.91,0.99
Comorbidities				
Infertility treatment	0.91	0.84, 0.99	0.93	0.86, 1.02
Hypothyroidism	0.92	0.85, 0.99	0.89	0.83, 0.96
PCOS	0.90	0.80, 1.00	0.88	0.78, 0.99
Hyperandrogenism	0.80	0.64, 1.00	0.77	0.62, 0.97
Metabolic syndrome	0.74	0.52, 1.03	0.71	0.50, 0.99
Obesity	1.16	1.09, 1.23	1.04	0.98, 1.10
Metformin use				
Any Use	1.00	0.92, 1.07	1.01	0.94, 1.09

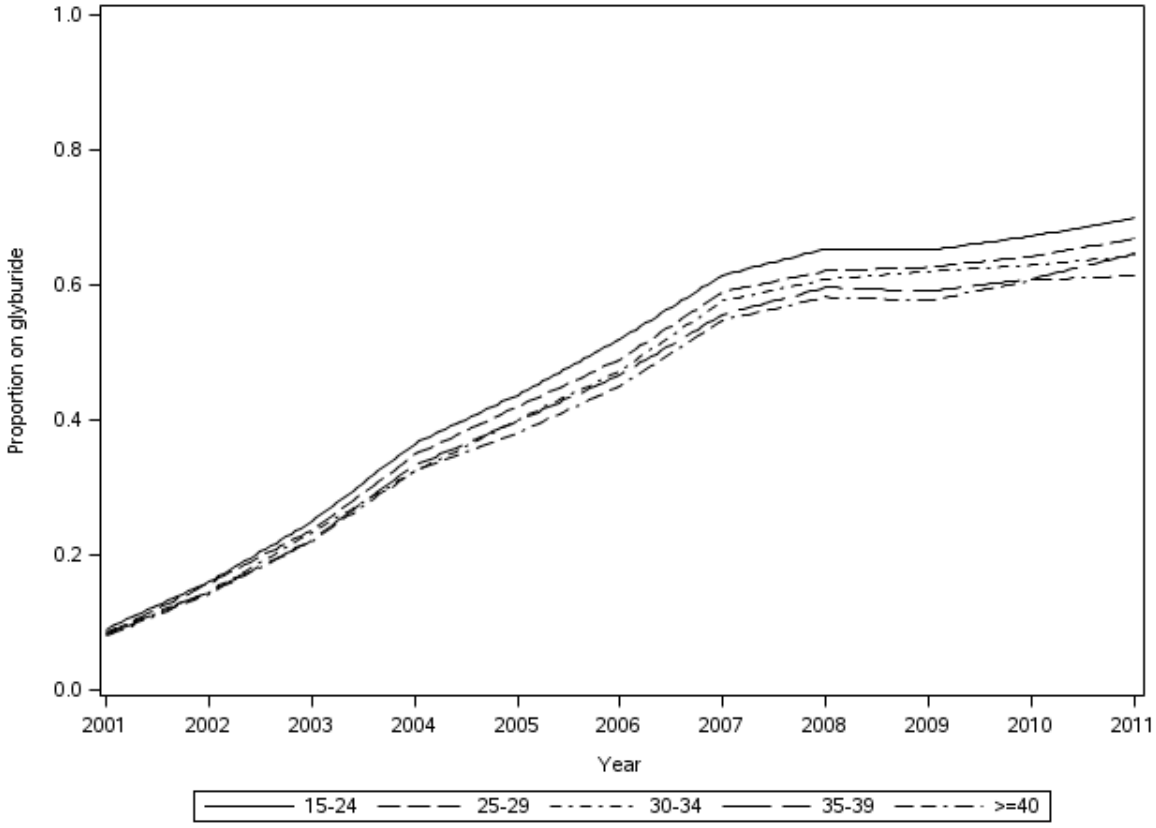
*All prevalence ratio estimates were adjusted for all other variables in the table.
†Reference category
‡PCOS- Polycystic Ovarian Syndrome

Table 6. Association of glucose tolerance test results and initiation of glyburide. Prevalence Ratios (95%Confidence Intervals) for 10 unit change in glucose values.

	Crude		Adjusted	
	PR	**95%CI**	**PR**	**95%CI**
Screening	1.00	0.95, 1.05	1.01	0.96, 1.07
Fasting	1.00	0.90, 1.11	1.00	0.90, 1.10
One Hour	0.99	0.93, 1.05	0.98	0.92, 1.04
Two Hour	1.02	0.96, 1.07	1.02	0.97, 1.08

Prevalence Ratios (PR) were estimated from multivariable Binomial regression analyses, mutually adjusted for age and maternal comorbidities (hypothyroidism, obesity) .PR were estimated in a subsample of the full cohort [Glyburide (N=224), Insulin (N=115)]

Figure 5. Trends of glyburide prescribing, by age group. Proportions were estimated from multivariable Binomial regression analyses, adjusted for all maternal comorbidities and prior metformin use.



CHAPTER VI- MANUSCRIPT 2

Effectiveness Of Glyburide Versus Insulin On Measures Of Adverse Maternal And Neonatal Outcomes in women with Gestational Diabetes

6.1 Introduction

The prevalence of gestational diabetes (GDM) in the United States (US) has more than doubled over the last 20 years (70, 71). Because uncontrolled hyperglycemia during pregnancy affects fetal development and neonatal adaptation, adequate treatment has a direct impact in preventing adverse maternal and perinatal outcomes (4). In 7-10% of women with GDM, routine care such as dietary measures, physical activity and glucose monitoring may not be enough to achieve glucose control. In this group, initiation of pharmacotherapy becomes the next step but evidence on the safety and effectiveness of available therapies is still scarce.

Insulin is the only pharmacological treatment endorsed by the American Diabetes Association (72) for the treatment of GDM in the United States (US). Due to its mechanism of action, ease of use and cost glyburide may be an appropriate first line treatment alternative. The study by Langer et al. in 2000 (17) was the first randomized controlled trial (RCT) to provide evidence on the efficacy of glyburide versus insulin in women with GDM. Since then two more RCTs (18, 19), several observational studies (20, 24, 91, 92) and meta-analyses (8, 23) have been conducted. Evidence from trials suggests that glyburide may be associated with poor outcomes such as neonatal jaundice, hypoglycemia and birth trauma. Less studied

outcomes have been large for gestational age and respiratory distress. Given its widespread use and rapid uptake of glyburide in the last decade, further evaluation of the association between adverse neonatal outcomes and use of glyburide is needed. The purpose of this study was to assess the effectiveness of glyburide compared to insulin in the treatment of gestational diabetes in a real world population.

6.2 Results

We identified 110,940 women with GDM and their babies, of whom 8.3% initiated pharmacotherapy. There were 4,986 (54.3%) women treated with glyburide and 4,194 treated with insulin. Characteristics of women at baseline appear in Table 1. The mean age was 33.5 [SD 4.7] years. The proportion of women treated with glyburide increased from 8.5% in 2000 to 64.4% in 2011. Obesity and preeclampsia were more common in the glyburide group, while hypothyroidism and infertility treatment were more common in women treated with insulin. There were no differences between groups in metformin use prior to the initiation of pharmacotherapy (Table 7).

Table 8 shows the crude and adjusted results for the risk of adverse maternal and neonatal outcomes in women initiated with glyburide when compared with insulin. We observed an increased risk of NICU admission (RR 1.39 95%CI 1.21, 1.59), respiratory distress (1.60 95%CI 1.21, 2.11), neonatal hypoglycemia (1.39 95%CI 1.00, 1.94), birth injury (1.36 95%CI 1.01, 1.8) and large for gestational age (1.43 95%CI 1.6, 1.76) among newborns whose mothers were treated with

glyburide. The risk of cesarean section was 3% lower in the glyburide group (RR 0.97 95%CI 0.93, 1.00). The absolute increase in risk was higher for admission to NICU (RD 2.9 95%CI 1.7, 4.0), large for gestational age (RD 1.4 95%CI 0.6, 2.2) and respiratory distress (RD 1.1 95%CI 0.5, 1.7) (Table 3). The corresponding numbers needed to harm were 35 (95%CI 25,59) for NICU admission, 71 (95%CI 46,165) for large for gestational age, and 94 (95%CI 59,220) for respiratory distress.

We conducted secondary analysis excluding women treated before 2004, 2005 or 2007 (Appendix 4). We chose these cutoffs based on the trends of use of glyburide reported by Camelo-Castillo et al. (REF PAPER 1). After excluding women in the earlier years the magnitude of the effects were attenuated for all outcomes, but remained elevated. In the years with better ascertainment of obesity, although the magnitude of the effect is lower when compared to the full cohort, the risk is still elevated for NICU admission (1.29 95%CI 1.11, 1.50), respiratory distress (RR 1.37 95%CI 1.01 1.87), hypoglycemia (1.12 95%CI0.79, 1.58), birth injury (1.16 95%CI 0.82, 1.64) and large for gestational age (RR 1.30 95%CI 1.02, 1.65). Changes in precision are due to a smaller number of outcomes. Estimates from models that were not adjusted and partially adjusted for obesity are presented in Appendix 5.

Because our result of an increased risk for respiratory distress and NICU admission with glyburide versus insulin differed most from the findings in trials and these outcomes are strongly associated with obesity, we used the array approach to estimate the 'true' RR for these two outcomes (Appendix 3-Figure A). To estimate the 'true' RR we assumed that the association between obesity and initiating glyburide versus insulin (RR Glyb-O) was RR 1.38, and the association between

obesity and respiratory distress (RR O-RDS) was 1.8, which are the magnitudes of effect observed in our population . Using this approach the 'true' RR for respiratory distress would be 1.55 where the bias in our partially adjusted estimates would be approximately 5%. In scenarios where the magnitude for RR Glyb-O is larger, the 'true' RR will be closer to 1.4 (holding RR O-RDS constant). For NICU admission, in our study the association between obesity and NICU (RR O-NICU) was 1.4. The 'true' association between glyburide and NICU admission was 1.36 where bias in our partially adjusted estimates would be 2.8% (Appendix 5-Figure B).

6.3 Discussion

In our population- based cohort of 9,180 women with gestational diabetes we found evidence of an increased risk of adverse events in those treated with glyburide when compared to insulin. Admission to the NICU, respiratory distress, hypoglycemia, birth injury and large for gestational age were more likely to occur among women treated with glyburide. Smaller differences between treatment groups were found for outcomes such as obstetric trauma, cesarean section, jaundice or preterm birth.

Previous literature on the association between treatment with glyburide and adverse neonatal outcomes is limited. To date, only three trials have assessed the safety or effectiveness of glyburide compared to insulin in pregnancy. The only outcomes reported by all trials were neonatal hypoglycemia and cesarean section (Figure 1). All studies found an elevated risk of neonatal hypoglycemia but the magnitude of the effect differed (18, 19). When compared with the RCTs, the

magnitude of our estimated effect was lower which could be explained by differences in the definition of the outcome. Our study identified newborns with hypoglycemia who required care in the NICU, while trials identified hypoglycemia cases based on blood glucose measurements. Given the controversy regarding choice of cutoff values to diagnose and treat neonatal hypoglycemia, our estimate may be more reflective of symptomatic hypoglycemia.

Only the trial by Langer et al reported estimates for outcomes such as NICU admission, respiratory distress and jaundice (17). Our findings differ from those published by Langer et al. for these outcomes. In their study the risk of NICU admission and respiratory distress was lower among newborns from glyburide treated women (RR 0.87 95%CI 0.41, 1.83 and RR=0.67 95%CI 0.19, 2.35, respectively). However, the trial was a single-site study with a standardized protocol for maternal and newborn care. Since criteria for admission to the NICU could vary across providers, our results could be more representative of practices related to newborn care across the United States. Compared to the trial our definition of respiratory distress identified critically ill infants and excluded less serious diagnoses such as transient tachypnea of the newborn. Therefore, our estimates for respiratory distress may be reflective of more severe conditions requiring NICU admission. The same principle applies to jaundice where the trial identified newborns based on predefined bilirubin cutoff values, while our study identified newborns with jaundice who required care in the NICU.

The risk of large for gestational age was 43% higher among newborns from glyburide treated women. In our study this outcome was defined through the use of

ICD9 codes. Because coding for this diagnosis may include both macrosomia or large for gestational age, our estimates could differ from those in trials. In the trials, large for gestational age had a prevalence of 5.7% (n=23) in the study by Langer, and 7.8% (n=4) in the study by Bertini. For macrosomia the prevalence was 12.4%(n=50) and 13.7% (n=7) for the study by Langer and Bertini, respectively. The prevalence in our study was 4.0% (n=368), which is closer to the prevalence of macrosomia reported in the trials. Our estimate is of lower magnitude but consistent with the estimates for macrosomia reported by Langer (RR 1.57 95%CI 0.70, 3.55) and Bertini (RR 10.1 95%CI 0.57, 178.0).

Birth injury and preterm birth were not assessed in the clinical trials. The observational studies by Jacobson et al. and Ramos et al. reported a higher risk of birth injury among those in the glyburide group (3.03 95%CI 0.81, 11.28; 3.55 95%CI 0.33,38.0)(20, 24). Although their population was largely Hispanic and insured by Medicaid, our estimates are more modest when compared to their findings. Regarding preterm birth, our findings are consistent with those reported by Jacobson et al. who found no difference between treatment groups (RR 0.97 95%CI 0.61, 1.54), but not with Ramos et al. who found an increased risk among women on glyburide (1.97 95%CI 0.87, 4.48). Given that by design the population in the study by Ramos had higher glucose values in both the screening and tolerance test, differences could be attributed to different risks across groups of women.

Absence of information on BMI could lead to residual confounding by BMI. To assess the impact of partially adjusting for a known confounder (diagnostic code for obesity), we compared estimates from models not adjusted and partially adjusted for

obesity. For outcomes such as obstetric trauma, cesarean section, jaundice and preterm birth we observed not much difference between the three models. The effect of partially adjusting for obesity is more evident for outcomes such as NICU admission, respiratory distress, hypoglycemia and large for gestational age where the estimate shifts closer to the null. This may be explained by differences in the strength of the association between obesity and the outcome. This is graphically depicted in Appendix 5 where we observe what the 'true' association would be in scenarios where the prevalence of obesity in the glyburide group is increased or where the strength of the association between obesity and the outcome is varied . In both figures our estimates are close to the 'true' RRs for the ranges of obesity-outcome association observed in our data, which are consistent with prior literature (REFS). In addition our findings are consistent with recent work published by Ogburn et al supporting the statement by Greenland in which adjusting for a binary mismeasured confounder reduces bias, but produces a measure of effect that lies between the crude and the true estimate (93). The underlying assumption is that the direction of the effect between the confounder and the outcome is the same for both treatment groups. There is no evidence to suggest that the effect of obesity on adverse outcomes would differ in women treated with glyburide versus insulin.

To our knowledge, our study is the largest US population–based study to date to assess the comparative effectiveness of glyburide in pregnancy. Limitations of our study include lack of information on race-ethnicity, measurement error for obesity and the potential for unmeasured confounding. Previous studies have shown heterogeneity in the risk of adverse neonatal events by race. However there is no

evidence on differences by race after women initiate pharmacological treatment. Patterns observed in our dataset can be considered as representative of patterns of care among the employed and insured in the United States, providing an advantage over clinical trials. When compared to self-report, ascertainment of initiation of treatment through pharmacy claims is substantially improved, although we are unable to ascertain initial dosage and dosage escalation which affect glucose control. Because maternal and neonatal outcomes are relatively rare, large claims databases provide a unique setting to study safety and effectiveness of medications in pregnancy.

Conclusion

After accounting for maternal comorbidities and risk factors for neonatal outcomes we found an elevated risk for NICU admissions, neonatal hypoglycemia, respiratory distress, birth injury and large for gestational age in women with GDM treated with glyburide compared with insulin. These results are in agreement with findings from prior studies and suggest that women on glyburide may not be achieving adequate glucose control.

6.4 Tables and Figures

Table 7. Baseline characteristics of women with gestational diabetes treated with pharmacotherapy, 2000-2011

		Insulin		Glyburide		
		N=4,194	%	N=4,986	%	%Δ*
Age, year- Mean(SD)		34 (4.7)		33 (4.8)		
Age, 5y categories						
	15-19	4	0.1	3	0.1	-0.04
	20-24	99	2.4	124	2.5	0.13
	25-29	730	17.4	940	18.9	1.45
	30-34	1593	38.0	1860	37.3	-0.68
	35-39	1292	30.8	1508	30.2	-0.56
	40-44	442	10.5	523	10.5	-0.05
	>=45	34	0.8	28	0.6	-0.25
Calendar year						
	2001	54	1.3	5	0.1	-1.19
	2002	115	2.7	20	0.4	-2.34
	2003	245	5.8	73	1.5	-4.38
	2004	366	8.7	188	3.8	-4.96
	2005	449	10.7	306	6.1	-4.57
	2006	409	9.8	374	7.5	-2.25
	2007	406	9.7	538	10.8	1.11
	2008	438	10.4	661	13.3	2.81
	2009	657	15.7	1003	20.1	4.45
	2010	563	13.4	928	18.6	5.19

2011	492	11.7	890	17.8	6.12
Region					
Northeast	639	15.2	525	10.5	-4.71
Northcentral	1163	27.7	1442	28.9	1.19
South	1529	36.5	1955	39.2	2.75
West	838	20.0	1037	20.8	0.82
Unknown	25	0.6	27	0.5	-0.05
Comorbidities					
Infertility treatment	283	6.7	280	5.6	-1.13
Hypothyroidism	349	8.3	353	7.1	-1.24
PCOS†	171	4.1	162	3.2	-0.83
Hyperandrogenism	67	1.6	99	2.0	0.39
Hyperprolactinemia	14	0.3	11	0.2	-0.11
Metabolic syndrome	30	0.7	20	0.4	-0.31
Obesity	305	7.3	499	10.0	2.74
Overweight	9	0.2	17	0.3	0.13
No comorbidities	3154	75.2	3773	75.7	0.47
Antihypertensive use	104	2.5	143	2.9	0.39
Preeclampsia hospitalization	219	5.2	325	6.5	1.30
Metformin use					
Any use before 1st Rx	293	7.0	345	6.9	-0.07

*%Δ –Difference in Percent † PCOS- Polycystic ovarian syndrome

Table 8. Risk Ratios (RR) and 95% confidence intervals (95%CI) for adverse maternal and neonatal outcomes in women with GDM treated with glyburide compared to insulin

	No. Events				Crude		IPTW*-Adjusted	
	Glyburide	%	Insulin	%	RR	95%CI	RR	95%CI
Obstetric trauma	111	2.2	102	2.4	0.92	0.70, 1.19	0.92	0.71, 1.20
Cesarean	2,526	50.7	2,201	52.5	0.97	0.93, 1.01	0.97	0.93, 1.00
NICU†	511	10.2	302	7.2	1.42	1.24, 1.63	1.39	1.21, 1.59
Respiratory distress	145	2.9	73	1.7	1.67	1.27, 2.21	1.60	1.21, 2.11
Hypo-glycemia	95	1.9	55	1.3	1.45	1.05, 2.02	1.39	1.00, 1.94
Jaundice	17	0.3	15	0.4	0.95	0.48, 1.91	0.94	0.47, 1.89
Birth injury	111	2.2	69	1.6	1.35	1.01, 1.82	1.36	1.01, 1.84
Preterm	474	9.5	371	8.8	1.08	0.94, 1.22	1.03	0.91, 1.18
Large for Gestational Age	234	4.7	134	3.2	1.47	1.19, 1.81	1.43	1.16, 1.76

Risk Ratios are adjusted for infertility treatment, hypothyroidism, polycystic ovarian syndrome, hyperandrogenism, metabolic syndrome, obesity, antihypertensive use and preeclampsia, using inverse probability of treatment weights. Calendar year was adjusted for in the risk model.

*IPTW-Inverse Probability of Treatment Weights

†NICU- Neonatal intensive care unit- Admission for >24 h for newborns requiring support.

Table 9. Risk differences and 95% confidence intervals (95%CI) for adverse maternal and neonatal outcomes in women with GDM treated with glyburide compared to insulin

	No. Events				Crude		IPTW-Adjusted	
	Glyburide	%	Insulin	%	RD	95%CI	RD	95%CI
Obstetric trauma	111	2.2	102	2.4	-0.21	-0.83, 0.42	-0.19	-0.81, 0.43
Cesarean	2,526	51	2,201	52	-1.81	-3.87, 0.24	-1.84	-3.89, 0.21
NICU	511	10	302	7.2	3.05	1.90, 4.20	2.85	1.69, 4.00
Respiratory distress	145	2.9	73	1.7	1.17	0.56, 1.78	1.07	0.46, 1.68
Hypo-glycemia	95	1.9	55	1.3	0.59	0.08, 1.11	0.53	0.02, 1.05
Jaundice	17	0.3	15	0.4	-0.02	-0.26, 0.23	-0.02	-0.26, 0.22
Birth injury	111	2.2	69	1.6	0.58	0.02, 1.14	0.60	0.03, 1.16
Preterm	474	9.5	371	8.8	0.66	-0.52, 1.85	0.30	-0.89, 1.49
LGA	234	4.7	134	3.2	1.50	0.71, 2.29	1.40	0.60, 2.20

Risk Differences are adjusted for infertility treatment, hypothyroidism, polycystic ovarian syndrome, hyperandrogenism, metabolic syndrome, obesity, antihypertensive use and preeclampsia, using inverse probability of treatment weights. Calendar year was adjusted for in the risk model.

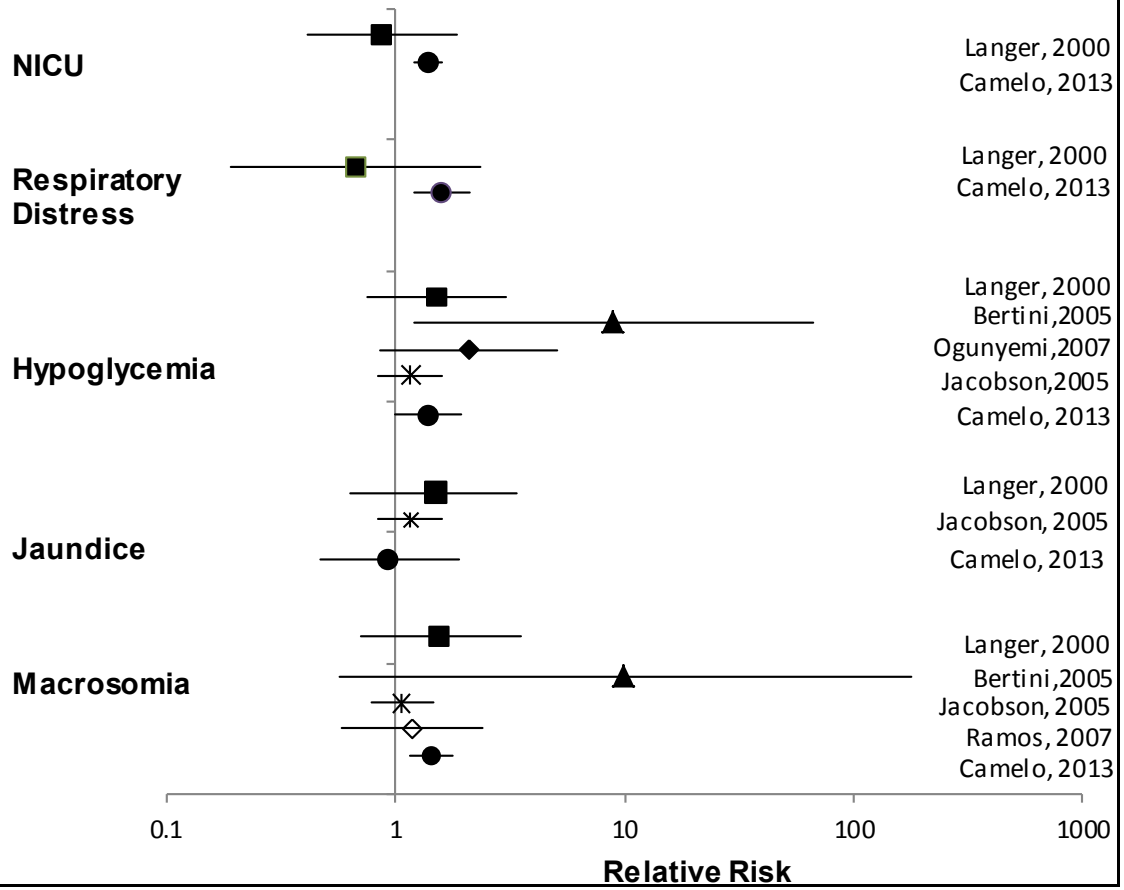
*IPTW-Inverse Probability of Treatment Weights

†NICU- Neonatal intensive care unit.

‡LGA – Large for Gestational Age

Figure 6. Comparison of Risk Ratios and 95%CI between randomized controlled trials and the present study.

	Glyburide	Insulin
Langer,2000	12/201	14/203
Camelo,2013	511/4986	302/4194
Langer,2000	4/201	6/203
Camelo, 2013	145/4986	73/4194
Langer,2000	18/201	12/203
Bertini,2005	8/24	1/27
Ogunyemi,2007	12/43	6/45
Jacobson, 2005	72/236	73/268
Camelo,2013	511/4986	302/4194
Langer,2000	12/201	8/203
Jacobson, 2005	59/236	58/268
Camelo,2013	17/4986	15/4194
Langer,2000	14/201	9/203
Bertini,2005	4/24	0/27
Jacobson, 2005	60/236	64/268
Ramos, 2007	10/44	15/78
Camelo,2013	234/4986	134/4194



CHAPTER VII-DISCUSSION

Prevalence of GDM has increased over the last decade, affecting reproductive age women across all ages. Due to the concomitant increase in insulin resistance and obesity, severity of the disease is also expected to be affected. One of the manifestations of severity is failure to achieve glucose control with interventions such as diet therapy and physical activity. Therefore the proportion of women that will require pharmacotherapy during pregnancy is expected to increase.

This project focused on describing the dissemination of glyburide use and channeling of treatment, as well as examining the effectiveness of glyburide compared to insulin and adverse outcomes. Use of glyburide in pregnancy started only in the last decade and in the US the rate of use and factors driving its prescription are unknown. Our first aim addresses this issue by describing trends of use of glyburide as well as the identification of predictors of treatment with glyburide. After addressing factors that could influence choice of medication, we compared the effectiveness of glyburide versus insulin by estimating the risk of adverse events that direct or indirectly reflect achievement of glucose control.

7.1 Summary of findings

Over the 2000-2011 period the annual percent increase in the use of glyburide was 19.4%. While in 2001 only 8.5% of the women on pharmacotherapy initiated glyburide, since 2008 this percentage has increased over 60%. Identification

of predictors of treatment with glyburide included maternal comorbidities associated with insulin resistance such as hypothyroidism, metabolic syndrome, obesity and PCOS. Overall women initiating glyburide were younger and less likely to be insulin resistant or obese.

Glucose values at screening or time of diagnosis (OGTT) do not seem to be associated with choice of medication. These results should be interpreted with caution since lab values were available for only a small proportion of women, and these women differed from the full cohort in their covariate distribution. Potentially glucose values at time of *initiation* are stronger predictors of drug class at initiation.

Because the distribution of comorbidities varied between treatment groups we used IPTW to adjust for confounding. After adjusting for covariates of interest our estimates showed an increased risk of admission to the NICU, hypoglycemia, respiratory distress, and large for gestational age among newborns from mothers treated with glyburide. We conducted sensitivity analysis to estimate the effect of women who were treated with glyburide in the early years, who may not be comparable to women treated after dissemination of treatment. Although the variability increased due to a reduction of the sample size, estimates of risk were consistent with previous results.

Given that obesity is a strong risk factor and there is potential for measurement error we conducted additional sensitivity analysis to estimate the effect of residual confounding for NICU admission and respiratory distress. The analyses showed that under the conditions observed in the study where there are

10% more obese women in the glyburide group, our estimate of risk is only slightly biased. For our estimates to cross the null, the strength of the confounder outcome association would have to be extreme and the proportion of women with obesity in the glyburide group would have to be higher than 30%.

7.2 Strengths and limitations

Limitations of our study include absence of information on gestational age, under ascertainment of obesity and absence of information on race-ethnicity. Claims databases usually do not have person level information such as last menstrual period or biometrics (such as height, weight). Information on gestational age would allow us to identify start of pregnancy and therefore have better ascertainment of the pre-pregnancy period. This is relevant for the identification of comorbidities and exclusion criteria such as pre-gestational type 1 or 2 diabetes. Because we also excluded women who had a prescription for insulin or glyburide more than 150 days before delivery, we were likely to capture pre-gestational type 1 or 2 diabetics that were not identified using ICD9 codes. Our approach to identify GDM is comparable to previously published validation studies where the misclassification due to absence of information on gestational age is small (87).

We used ICD9 codes to ascertain obesity in our study. Because occurrence of codes is related to reimbursement, codes for obesity may be underutilized unless a procedure requiring the code is being billed for. Additionally, since 2006 new codes were included more specific to defined ranges of BMI. The use of these codes is expected to rise as reimbursement policies that require these codes start taking

place. Therefore we expect under ascertainment of obesity, especially before 2006. Even though our measure of obesity has error we do not expect it to be differential between treatment groups. Because our data is de-identified a validation study for obesity was not feasible.

Racial and ethnic differences in treatment and risk of adverse outcomes have been described previously. Treatment may be affected by access to healthcare as well as individual preferences, or providers perception of risk. Additionally clinical characteristics of women with GDM, such as obesity, may vary across different races and ethnic groups. Heterogeneity across races in the response to pharmacological therapy along with interaction with other comorbidities may explain differences between groups. Due to absence of personal identifiers such as race, this issue was not explored and is outside the scope of this study.

Strengths are ascertainment of medication use, sample size and generalizability. Ascertainment of medication use in administrative databases is thought to be more accurate than self-report. Because we were interested in initiation of medication and timing is key to identify 'true' GDM, pharmacy claims associated with prescription fills become reliable source to ascertain time of initiation. Our ability to address the effects of dose at initiation or dose escalation is limited due to absence of this information in the data.

Among the RCTs and observational studies published to date, our study is the largest and most reflective of the use of glyburide and insulin for GDM at the population level. Because adverse maternal and neonatal outcomes are relatively

rare, a large sample size allows us to observe such outcomes. Given that our population is not hospital based we are more likely to capture differences in characteristics of women with GDM as well as variations in GDM management across the United States, which may impact outcomes. Our data are representative of higher density population areas which is reflected in the large proportion of women in urban settings. Overall our study population can be considered as being reflective of the US population.

7.3 Public Health Implications

We provide evidence on the widespread use of glyburide for the treatment of GDM in the US. Although use of glyburide was expected to increase throughout the decade, it has surpassed insulin as therapy of choice. Currently there are no available recommendations providing guidance for treatment with glyburide. A reflection of this is the absence of strong drivers for treatment with glyburide among covariates assessed in the study. It is possible that other factors such as personal preference, provider experience or perception of risk influence this decision. Additionally in other subgroups not included in this study, access to healthcare and cost of medications may also play an important role.

A higher risk of neonatal outcomes among glyburide treated women demands further attention. Prevention of neonatal outcomes has short term impact in terms of morbidity and costs of care. In addition, recent studies have started to link metabolic disturbances in the neonatal period to the risk of insulin resistance or obesity in childhood or adulthood (94, 95). Clinically this implies that better management of

women treated with glyburide is needed. There is need for evidence based recommendations that provide guidance relative to dosing, and that help identify of women more likely to benefit from glyburide.

7.4 Conclusions

In conclusion we present evidence of higher risk of adverse outcomes in women with GDM treated with glyburide when compared to insulin, in the US. Because dissemination of glyburide is high, clinicians should be aware of its effectiveness when compared to insulin. Closer follow-up after initiation of glyburide may allow earlier identification of women not benefiting from therapy. Design and implementation of guidelines for management of GDM with glyburide is a priority in this population.

APPENDIX 1. ICD9 and CPT codes used to identify deliveries

Diagnosis	Code	Code type	Description
Delivery	V27.0	ICD9	Single liveborn
	V27.9	ICD9	Unspecified outcome of deliver
	650	ICD9	Normal delivery

Procedure	Code	Code type	Description
Cesarean Section	59510	CPT	Routine obstetric care including antepartum care, cesarean delivery and postpartum care
	59514	CPT	Cesarean only
	59515	CPT	Cesarean only, including postpartum care
	740	ICD9P	Classical c-section
	741	ICD9P	Low cervical c-section
	742	ICD9P	Extraperitoneal c-section
	744	ICD9P	C-section of other specified type
	749	ICD9P	C-section unspecified type
	7499	ICD9P	Other c-section
Vaginal	59400	CPT	Routine obstetric care, vaginal del (w-w/o episiotomy or forceps) and postpartum care
	59409	CPT	Vaginal del only (w-w/o episiotomy or forceps)
	59410	CPT	Vaginal del only + postpartum care
	59412	CPT	External cephalic version
Vaginal after previous cesarean	59610	CPT	Routine obstetric care including antepartum care, cesarean delivery and postpartum care, after previous cesarean delivery
	59612	CPT	Vaginal del only after previous c-section (w-w/o episiotomy or forceps)
	59614	CPT	Vaginal del only after previous c-section (w-w/o episiotomy or forceps) , including postpartum care
	59618	CPT	Routine obstetric care including antepartum care, cesarean delivery and postpartum care, following attempted vaginal del, after previous cesarean delivery
	59620	CPT	Cesarean del only, following attempted vag del after prev c-section
	59622	CPT	Cesarean del only, following attempted vag del after prev c-section; including postpartum care

APPENDIX 2- ICD9 and CPT codes used to identify outcomes

Obstetric Trauma	664.2	ICD9	Third-degree perineal laceration
	664.20	ICD9	Third-degree perineal laceration unspecified as to episode of care or not applicable
	664.21	ICD9	Third-degree perineal laceration delivered, with or without mention of antepartum condition
	664.24	ICD9	Third-degree perineal laceration postpartum condition or complication
	664.3	ICD9	Fourth-degree perineal laceration
	664.30	ICD9	Fourth-degree perineal laceration unspecified as to episode of care or not applicable
	664.31	ICD9	Fourth-degree perineal laceration delivered, with or without mention of antepartum condition
	664.34	ICD9	Fourth-degree perineal laceration postpartum condition or complication
	665	ICD9	Other obstetrical trauma
	665.3	ICD9	Laceration of cervix
	665.30	ICD9	Laceration of cervix unspecified as to episode of care or not applicable
	665.31	ICD9	Laceration of cervix delivered, with or without mention of antepartum condition
	665.34	ICD9	Laceration of cervix postpartum condition or complication
	665.4	ICD9	High vaginal laceration
	665.41	ICD9	High vaginal laceration delivered, with or without mention of antepartum condition
	665.44	ICD9	High vaginal laceration postpartum condition or complication
	75	ICD9P	Other obstetric operations
	75.5	ICD9P	Repair of current obstetric laceration of uterus
	75.50	ICD9P	Repair of current obstetric laceration of uterus, not otherwise specified
	75.51	ICD9P	Repair of current obstetric laceration of cervix
	75.52	ICD9P	Repair of current obstetric laceration of corpus uteri
	75.6	ICD9P	Repair of other current obstetric laceration
	75.61	ICD9P	Repair of current obstetric laceration of bladder and urethra
	75.62	ICD9P	Repair of current obstetric laceration of rectum and sphincter ani
	75.69	ICD9P	Repair of other current obstetric laceration

Cesarean	59510	CPT	Routine obstetric care including antepartum care, cesarean delivery and postpartum care
	59514	CPT	Cesarean only
	59515	CPT	Cesarean only, including postpartum care
	740	ICD9P	Classical c-section
	741	ICD9P	Low cervical c-section
	742	ICD9P	Extraperitoneal c-section
	744	ICD9P	C-section of other specified type
	749	ICD9P	C-section unspecified type
	7499	ICD9P	Other c-section
	59618	CPT	Routine obstetric care including antepartum care, cesarean delivery and postpartum care, following attempted vaginal del, after previous cesarean delivery
	59620	CPT	Cesarean del only, following attempted vag del after prev c-section
	59622	CPT	Cesarean del only, following attempted vag del after prev c-section; including postpartum care

NICU admission	99295	CPT	First day of NICU，neborns
	99468	CPT	Critical care code – Initial day
	99477	CPT	Intensive care services- Initial day neonates

Respiratory Distress	770.84	ICD9	Respiratory failure of newborn
	770.87	ICD9	Respiratory arrest of newborn
	770.89	ICD9	Other respiratory problems after birth
	770.9	ICD9	Unspecified respiratory condition of fetus and newborn

Hypo-glycemia	775.6	ICD9	Neonatal Hypoglycemia
	775.0	ICD9	Syndrome of Infant of diabetic mother

Jaundice	36450	CPT	Exchange transfusion blood, newborn
	9983	ICD9P	Phototherapy (bilirubin) light with photometer
	9982	ICD9P	Phototherapy (bilirubin) -uv
	7741	ICD9	Othe jaundice from excessive hemolysis
	7745	ICD9	Perinatal jaundice from other causes
	7746	ICD9	Unspecified fetal and neonatal jaundice

Birth Trauma	653.4	ICD9	Fetopelvic disproportion
	653.41	ICD9	Fetopelvic disproportion delivered, with or without mention of antepartum condition
	653.42	ICD9	Fetopelvic disproportion delivered, with mention of postpartum complication
	653.44	ICD9	Fetopelvic disproportion postpartum condition or complication
	653.5	ICD9	Unusually large fetus causing disproportion
	653.51	ICD9	Unusually large fetus causing disproportion delivered, with or without mention of antepartum condition
	653.52	ICD9	Unusually large fetus causing disproportion delivered, with mention of postpartum complication
	660.4	ICD9	Shoulder (girdle) dystocia
	660.41	ICD9	Shoulder (girdle) dystocia delivered, with or without mention of antepartum condition
	660.42	ICD9	Shoulder (girdle) dystocia delivered, with mention of postpartum complication
	660.44	ICD9	Shoulder (girdle) dystocia postpartum condition or complication
	767	ICD9	Birth trauma
	767.0	ICD9	Subdural and cerebral hemorrhage
	767.1	ICD9	Injuries to scalp
	767.11	ICD9	Epicranial subaponeurotic hemorrhage (massive)
	767.19	ICD9	Other injuries to scalp
	767.2	ICD9	Fracture of clavicle
	767.3	ICD9	Other injuries to skeleton
	767.4	ICD9	Injury to spine and spinal cord
	767.5	ICD9	Facial nerve injury
	767.6	ICD9	Injury to brachial plexus
	767.7	ICD9	Other cranial and peripheral nerve injuries
	767.8	ICD9	Other specified birth trauma
	767.9	ICD9	Birth trauma, unspecified
	959	ICD9	Injury, other and unspecified

	959.0	ICD9	Head, face and neck
	959.01	ICD9	Head injury, unspecified
	959.09	ICD9	Injury of face and neck
	959.1	ICD9	Trunk
	959.11	ICD9	Other injury of chest wall
	959.12	ICD9	Other injury of abdomen
	959.13	ICD9	Fracture of corpus cavernosum penis
	959.14	ICD9	Other injury of external genitals
	959.19	ICD9	Other injury of other sites of trunk
	959.2	ICD9	Shoulder and upper arm
	959.3	ICD9	Elbow, forearm, and wrist
	959.4	ICD9	Hand, except finger
	959.5	ICD9	Finger
	959.6	ICD9	Hip and thigh
	959.7	ICD9	Knee, leg, ankle, and foot
	959.8	ICD9	Other specified sites, including multiple
	959.9	ICD9	Unspecified site

Preterm	765.1	ICD9	Other preterm infants
	765.10	ICD9	Other preterm infants unspecified [weight]
	765.11	ICD9	Other preterm infants less than 500 grams
	765.12	ICD9	Other preterm infants 500-749 grams
	765.13	ICD9	Other preterm infants 750-999 grams
	765.14	ICD9	Other preterm infants 1,000-1,249 grams
	765.15	ICD9	Other preterm infants 1,250-1,499 grams
	765.16	ICD9	Other preterm infants 1,500-1,749 grams
	765.17	ICD9	Other preterm infants 1,750-1,999 grams
	765.18	ICD9	Other preterm infants 2,000-2,499 grams
	765.19	ICD9	Other preterm infants 2,500 grams and over
	765.21	ICD9	Less than 24 completed weeks of gestation
	765.22	ICD9	24 weeks of gestation
	765.23	ICD9	25-26 weeks of gestation
	770.84	ICD9	Respiratory failure of newborn
	770.87	ICD9	Respiratory arrest of newborn

	770.89	ICD9	Other respiratory problems after birth
	770.9	ICD9	Unspecified respiratory condition of fetus and newborn

LGA	766.0	ICD9	Exceptionally large baby
	7661	ICD9	Other heavy for dates infants
	656.6	ICD9	Excessive fetal growth

APPENDIX 3- Characteristics of women with laboratory results, 2007-2011

	Insulin		Glyburide		
	N=115	%	N=224	%	%Δ
Age, year- Mean(SD)	35 (4.9)		34 (4.8)		
Age, 5y categories					
15-19	3	2.6	8	3.6	1.0
20-24	18	15.7	34	15.2	-0.5
25-29	33	28.7	72	32.1	3.4
30-34	48	41.7	80	35.7	-6.0
35-39	22	19.1	28	12.5	-6.6
40-44	2	1.7	2	0.9	-0.8
>=45		0.0	0	0.0	0.0
Calendar year					
2007	7	6.1	5	2.2	-3.9
2008	7	6.1	28	12.5	6.4
2009	43	37.4	63	28.1	-9.3
2010	32	27.8	72	32.1	4.3
2011	26	22.6	56	25.0	2.4
Region					
Northeast	17	14.8	19	8.5	-6.3
Northcentral	17	14.8	38	17.0	2.2
South	63	54.8	130	58.0	3.3
West	18	15.7	37	16.5	0.9
Unknown	0	0.0	0	0.0	0.0
Comorbidities					
Infertility treatment	7	6.1	7	3.1	-3.0
Hypothyroidism	15	13.0	23	10.3	-2.8
PCOS	6	5.2	7	3.1	-2.1
Hyperprolactinemia	1	0.9	1	0.4	-0.4
Hyperandrogenism	2	1.7	2	0.9	-0.8
Metabolic syndrome	1	0.9	1	0.4	-0.4
Obesity	22	19.1	42	18.8	-0.4
overweight	0	0.0	2	0.9	0.9
No comorbidities	74	64.3	154	68.8	4.4
Metformin use					
Any Use before first RX	6	5.2	17	7.6	2.4

*Difference in percentage (Δ%)-Estimated by subtracting percentages in insulin column from glyburide. †PCOS- Polycystic Ovarian Syndrome

APPENDIX 4- Sensitivity Analysis: restriction by year of entry

					Crude			IPTW-Adjusted		
			N	No. Events	RR	95%CI		RR	95%CI	
Obstetric trauma	No exclusion	Glyburide	4986	111	0.92	0.70	1.19	0.92	0.71	1.20
		Insulin	4194	102						
	2004-2011	Glyburide	4884	107	1.00	0.75	1.32	1.00	0.75	1.33
		Insulin	3777	83						
	2005-2011	Glyburide	4696	101	1.02	0.76	1.37	1.02	0.75	1.37
		Insulin	3411	72						
	2007-2011	Glyburide	4020	87	1.01	0.72	1.40	0.99	0.71	1.39
		Insulin	2556	55						
Cesarean	No exclusion	Glyburide	4986	2526	0.97	0.93	1.01	0.97	0.93	1.00
		Insulin	4194	2201						
	2004-2011	Glyburide	4884	2476	0.96	0.92	1.00	0.97	0.93	1.01
		Insulin	3777	1987						
	2005-2011	Glyburide	4696	2390	0.96	0.92	1.00	0.96	0.92	1.00
		Insulin	3411	1813						
	2007-2011	Glyburide	4020	2041	0.95	0.90	0.99	0.96	0.91	1.00
		Insulin	2556	1370						

					Crude			IPTW-Adjusted		
			N	No. Events	RR	95%CI		RR	95%CI	
NICU	No exclusion	Glyburide	4986	511	1.42	1.24	1.63	1.39	1.21	1.59
		Insulin	4194	302						
	2004-2011	Glyburide	4884	503	1.37	1.19	1.57	1.34	1.17	1.55
		Insulin	3777	284						
	2005-2011	Glyburide	4696	494	1.36	1.18	1.57	1.34	1.16	1.55
		Insulin	3411	264						
	2007-2011	Glyburide	4020	458	1.30	1.12	1.51	1.29	1.11	1.50
		Insulin	2556	224						
Respiratory distress	No exclusion	Glyburide	4986	145	1.67	1.27	2.21	1.60	1.21	2.11
		Insulin	4194	73						
	2004-2011	Glyburide	4884	143	1.56	1.18	2.06	1.50	1.13	1.99
		Insulin	3777	71						
	2005-2011	Glyburide	4696	140	1.54	1.15	2.06	1.49	1.11	2.00
		Insulin	3411	66						
	2007-2011	Glyburide	4020	127	1.39	1.02	1.89	1.37	1.01	1.87
		Insulin	2556	58						
Hypoglycemia	No exclusion	Glyburide	4986	95	1.45	1.05	2.02	1.39	1.00	1.94
		Insulin	4194	55						
	2004-2011	Glyburide	4884	95	1.39	0.99	1.93	1.34	0.96	1.87
		Insulin	3777	53						
	2005-2011	Glyburide	4696	94	1.34	0.95	1.88	1.30	0.93	1.83
		Insulin	3411	51						
	2007-2011	Glyburide	4020	88	1.14	0.81		1.12	0.79	1.58
		Insulin	2556	49						

					Crude			IPTW-Adjusted		
			N	No. Events	RR	95%CI		RR	95%CI	
Jaundice	No exclusion	Glyburide	4986	17	0.95	0.48	1.91	0.94	0.47	1.89
		Insulin	4194	15						
	2004-2011	Glyburide	4884	17	0.94	0.46	1.90	0.94	0.46	1.91
		Insulin	3777	14						
	2005-2011	Glyburide	4696	17	0.95	0.46	1.95	0.95	0.46	1.95
		Insulin	3411	13						
	2007-2011	Glyburide	4020	17	0.83	0.40	1.71	0.83	0.40	1.71
		Insulin	2556	13						
Birth injury	No exclusion	Glyburide	4986	111	1.35	1.01	1.82	1.36	1.01	1.84
		Insulin	4194	69						
	2004-2011	Glyburide	4884	111	1.32	0.98	1.79	1.32	0.98	1.80
		Insulin	3777	65						
	2005-2011	Glyburide	4696	104	1.30	0.95	1.79	1.31	0.95	1.81
		Insulin	3411	58						
	2007-2011	Glyburide	4020	90	1.17	0.83	1.65	1.16	0.82	1.64
		Insulin	2556	49						

					Crude			IPTW-Adjusted		
			N	No. Events	RR	95%CI		RR	95%CI	
Preterm	No exclusion	Glyburide	4986	474	1.08	0.94	1.22	1.03	0.91	1.18
		Insulin	4194	371						
	2004-2011	Glyburide	4884	463	1.08	0.95	1.24	1.04	0.91	1.19
		Insulin	3777	331						
	2005-2011	Glyburide	4696	442	1.06	0.92	1.22	1.03	0.89	1.18
		Insulin	3411	303						
	2007-2011	Glyburide	4020	391	1.09	0.93	1.27	1.06	0.91	1.24
		Insulin	2556	228						
Large for Gestational Age	No exclusion	Glyburide	4986	234	1.47	1.19	1.81	1.43	1.16	1.76
		Insulin	4194	134						
	2004-2011	Glyburide	4884	228	1.39	1.12	1.72	1.36	1.10	1.68
		Insulin	3777	127						
	2005-2011	Glyburide	4696	221	1.34	1.08	1.66	1.31	1.05	1.63
		Insulin	3411	120						
	2007-2011	Glyburide	4020	200	1.32	1.04	1.68	1.30	1.02	1.65
		Insulin	2556	96						

In the 2007-2011 cohort we estimated the effect of treatment with glyburide on maternal and neonatal outcomes with obesity treated as an unmeasured confounder. To do this we excluded obesity from the propensity score model and estimated inverse probability of treatment weights. We used these weights to adjust for other confounders in the model and estimated Risk Ratios and 95%CIs.

APPENDIX 5- Sensitivity analysis: Unmeasured confounding

In the 2007-2011 cohort we estimated the effect of treatment with glyburide on respiratory distress and NICU admission with obesity treated as an unmeasured confounder. To do this we excluded obesity from the propensity score model and estimated inverse probability of treatment weights. We used these weights to adjust for other confounders in the model and estimated the effect on respiratory distress (RR_{RDS}) and NICU admission (RR_{NICU}). The results from these analysis are depicted in Figures A and B. We compared estimates obtained from the unmeasured confounding model with estimates obtained in our fully adjusted model.

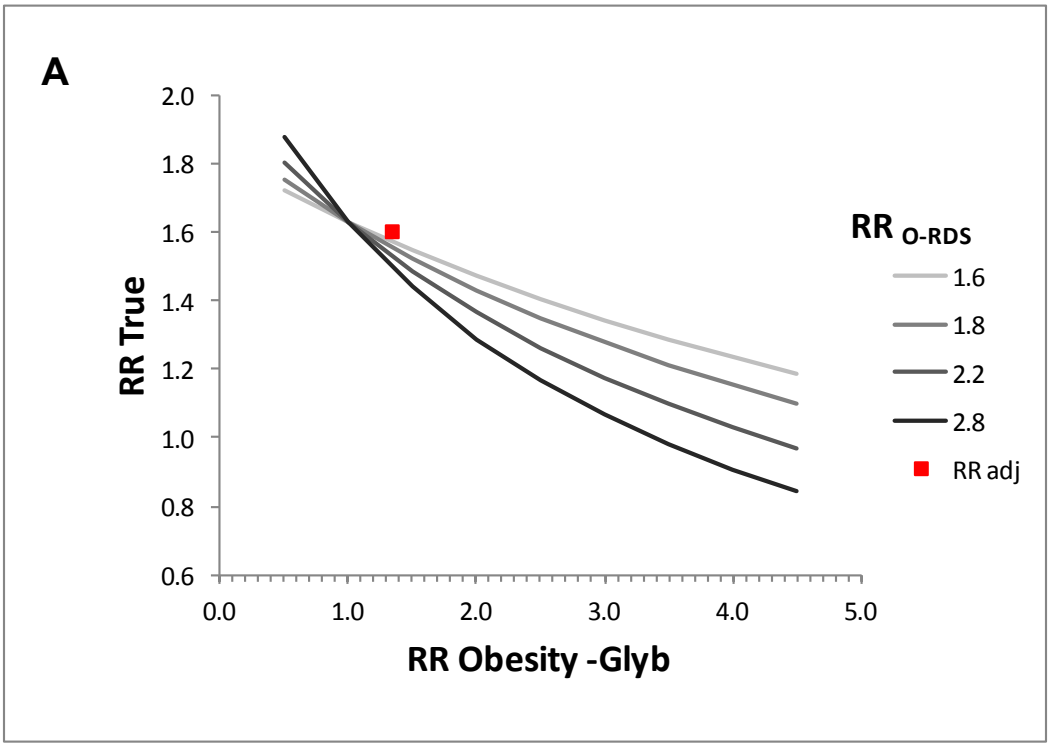


Figure A- Respiratory distress: in the unmeasured confounder scenario the apparent relative risk for respiratory distress (ARR_{RDS}) is 1.63, when the proportion of obesity is equal among treatment groups. If the prevalence of obesity increases in the glyburide group then

the ARR_{RDS} will shift towards the null. The decline of the ARR_{RDS} will be steeper as the strength of the association between obesity and respiratory distress increases ($RR_{O\text{-}RDS}$). The red square represents the RR estimate from the adjusted model that included obesity in the propensity score. Based on previously published studies it is unlikely that the prevalence of obese women in the glyburide group would be more than two times the prevalence in the insulin group.

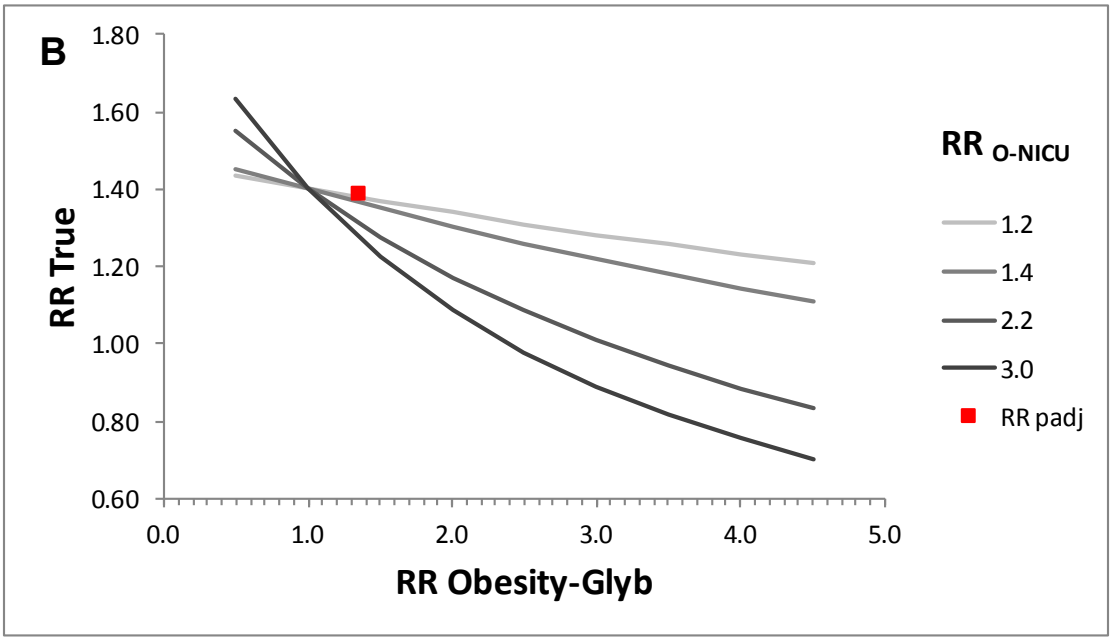


Figure B- NICU admission- the apparent relative risk for NICU admission (ARR_{NICU}) is 1.40, which is the observed effect in our study when obesity is not accounted for in the propensity score. As the prevalence of obesity increases in the glyburide group ($RR_{Obesity\text{-}Glyb}$), ARR_{NICU} shifts towards the null. This shift is steeper when the magnitude of $RR_{O\text{-}NICU}$ is higher. Our adjusted estimate (RR_{adj}) is represented by the red square ($RR_{Glyb\text{-}O}$=1.38).

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