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Review

Glyburide for the treatment of gestational diabetes mellitus

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Abstract:
Insulin is the traditional treatment for gestational diabetes mellitus (GDM) unresponsive to dietary interventions. Until recently, oral hypoglycemic drugs had been contraindicated due to concerns regarding teratogenicity and the possibility of neonatal hypoglycemia.
In contrast to other sulfonylurea drugs, *in vitro* and *in vivo* investigations have demonstrated very low transplacental transport of glyburide to the fetal circulation. The mechanisms preventing glyburide from crossing the human placenta are not completely understood. A combination of extremely high protein binding and a relatively short elimination half-life might partially explain it. It has also been demonstrated that glyburide is effluxed from the fetal to the maternal circulation by the breast cancer resistance protein (BRCP) and the human multidrug resistance protein 3 (MRP3).
Since 2000, several studies have reported an 80–85% success rate of glyburide treatment. However, some authors have noticed a glyburide-related increased risk of preeclampsia, macrosomia, neonatal hypoglycemia, admission to a neonatal intensive care unit and need for phototherapy. These possible maternal as well as neonatal adverse outcomes warrant further investigations. Until that time, the use of glyburide should remain inadvisable in pregnancy.

Key words:
glyburide, gestational diabetes mellitus, pregnancy, transplacental transport

Abbreviations: ACOG – American College of Obstetricians and Gynecologists, ATP – adenosine 5'-triphosphate, BRCP – breast cancer resistance protein, FDA – Food and Drug Administration, GDM – gestational diabetes mellitus, HSA – human serum albumin, Km – Michaelis-Menten constant, MRP – human multidrug resistance protein, NICU – neonatal intensive care unit, P-gP – P-glycoprotein, pKa – dissociation constant, Vmax – maximum velocity

Introduction

Gestational diabetes mellitus (GDM) complicates 2% to 5% of all pregnancies and is associated with the increased fetal as well as maternal morbidity and mortality [28]. Clinical recognition and adequate treatment

of women with significant hyperglycemia during pregnancy is important to minimize neonatal complications associated with GDM, including macrosomia, shoulder dystocia, hypoglycemia, polycythemia, hyperbilirubinemia, hypocalcemia and respiratory depression [12]. Hyperglycemia may lead to neuronal injury, atherogenesis and endothelial dysfunction [7, 10, 61].

Although in the majority of women glycemia is adequately controlled with diet and exercise, approximately 30% to 40% of them require pharmacological treatment. Traditional management of women with GDM in whom diet therapy fails involves the subcutaneous insulin administration [28]. This is the preferred pharmacological treatment in pregnancy because of the documented high efficacy and the fact that the insulin molecule due to its large molecular weight (6000 Da) cannot cross the placental barrier. Nevertheless, insulin can be transported across the human placenta as a part of the antibody-insulin complex [49]. The development of anti-insulin antibodies is one of possible risks of anti-insulin injections. Balsells et al. [2] and Weiss et al. [62] observed anti-insulin antibody production in response to human insulin in women with GDM. This autoimmune reaction to exogenous insulin treatment could also affect fetal growth [2].

The insulin therapy has several disadvantages including patient's discomfort, pain, inconvenience of injections and the increased cost [12]. Therefore, finding of an effective alternative to insulin is desirable for pregnant patients and their doctors.

Until recently, oral hypoglycemic agents had been avoided in pregnancy due to their potential to cause teratogenicity as well as fetal hyperinsulinemia and hypoglycemia [45, 64].

Since the 1990s metformin has mostly been studied during pregnancy, principally in the first 12 weeks of gestation in patients with polycystic ovary syndrome (PCOS). Preliminary studies have shown that in women with PCOS, metformin may be safe and may reduce risk of miscarriage and development of GDM when used for the entire pregnancy [23, 37]. Metformin may also have a role in therapy for GDM. A randomized controlled trial evaluating metformin treatment compared with insulin in 750 women with GDM is underway in New Zealand and Australia [57].

Despite the fact that the Food and Drug Administration (FDA) does not approve glyburide for the treatment of GDM, some experts and expert organizations in the United States (e.g., the Fifth International Workshop on Gestational Diabetes and the North American Diabetes in Pregnancy Study Group) have endorsed the use of glyburide as an alternative pharmacological therapy to insulin during pregnancy [12, 17, 24, 25, 50, 56]. Glyburide is currently classified as Category B by the FDA for use in pregnancy, which means that there is no evidence of risk in humans. In 2001, the American College of Obstetricians and Gynecologists (ACOG) advocated caution in adopting oral agents as an acceptable modality for management of GDM [1]. This specialty body noticed that further studies are needed in a large patient population to establish the safety criteria. In 2004, the ACOG reported that 13% of 1400 American obstetricians used glyburide as first-line therapy in the case of failure of dietary intervention in women diagnosed with GDM [18]. At the population level, a recent abstract reported that 16% of women with the need for medical treatment in pregnancy received oral agents [5].

The rationale for the use of glyburide during pregnancy is based on the similarities of the pathophysiology of GDM and type 2 diabetes. Sulfonylurea drugs have been used to treat type 2 diabetes for many decades and require functional pancreatic β-cells for their hypoglycemic effect. They appear to act by inhibiting potassium efflux *via* adenosine 5'-triphosphate (ATP) dependent potassium channels [60]. This action leads to cellular depolarization and calcium-stimulated release of insulin in pancreatic β-cells [21]. The primary effect of these drugs is enhancement of insulin secretion, which suppresses the main contributor to fasting hyperglycemia, i.e. hepatic glucose production [25, 26]. Sulfonylurea drugs diminish glucose toxicity and improve insulin secretion after meals, thus reducing postprandial hyperglycemia. Studies have demonstrated that these drugs can also enhance peripheral tissue sensitivity to insulin [11, 52].

Glyburide (also known as glibenclamide) manifests large individual variation with respect to its pharmacokinetics and pharmacodynamics [38, 44, 53]. In subjects with normal renal and liver function, the apparent oral clearance of glyburide is reported to range from 11.2 to 230 l/h, with an elimination half-life estimated at about 4 h [34, 44]. The drug is extensively metabolized by human hepatic microsomes to form its two major metabolites, 4-trans- and 3-cis-hydroxycyclohexyl glyburide, which are excreted in bile and urine to equal extent [33, 54, 55].

Jain et al. [29] investigated the role of human placenta in biotransformation of glyburide. The forma-

tion of metabolites by microsomal fractions obtained from placentas of healthy pregnancies in the presence of increasing concentrations of glyburide exhibited typical Michaelis-Menten kinetics. Analysis of the saturation curves obtained from placentas revealed apparent Michaelis-Menten constant (Km) values for the drug that were similar to those determined for human liver microsomes. However, maximum velocity (Vmax) for product formation in the presence of placental microsomes varied widely between individuals and was almost 1/1000 of that determined for the liver enzymes [29]. Ravindran et al. [47] identified glyburide metabolites formed by placental microsomes of humans and baboons as the 4-cis-, 3-trans- and 2-trans-hydroxycyclohexyl glyburide.

Transplacental transport

Similarly to other epithelial barriers, transfer of substances across the placenta is controlled by such factors as molecular weight (only < 1000 Da), dissociation constant (pKa), lipophilicity, placental blood flow, blood protein binding, distribution volume and elimination half-life [19, 34].

Using an *in vitro* single human cotyledon perfusion model, Elliott et al. [14] demonstrated that the maternal-to-fetal transport of glyburide achieved an average of fetal concentration of 26 ng/ml at 2 h, when the original maternal concentration was 1000 ng/ml. This maternal concentration is 3- to 8-fold higher than the therapeutic peak levels after a 5 mg oral dose in humans. Results of a large clinical trial by Langer et al. [39] confirmed the above-mentioned glyburide placental transfer. In that study in 13 cases, timed blood samples showed maternal glyburide concentration ranging from 50 to 150 ng/ml while cord blood levels of glyburide were undetectable with high-performance liquid chromatographic analysis.

In 1994, Elliott et al. [15] used again the *in vitro* placental perfusion model to characterize the rates of placental transfer of four sulfonylurea derivatives (two old medications i.e. chlorpropamide and tolbutamide, and two newer ones i.e. glipizide and glyburide). Employing a perfusate with 2 g/l albumin, they found that within 2 h of perfusion, the rate for transplacental transfer of glyburide was approximately 50% of that of glipizide, 20% of that of chlorpropamide, and 10% of that of tolbutamide. Researchers compared dissociation constants and lipid solubility, but could not find a relationship, possibly because of the fact that all four drugs have relatively similar pKa (i.e. 4.8–5.9) and the log octanol/water partition coefficient [15]. In fact, glyburide has the highest lipid solubility and the least transferability.

The mechanisms for the minimal placental passage of this small molecule are not clear. However, glyburide with a molecular weight of 494 is one of the largest oral hypoglycemic agents [22]. Lack of its significant appearance in the fetal circulation could also result from a very high protein binding of the drug because Elliot et al. [15] added albumin in the experiment. All four hypoglycemics examined have high protein binding, above 96%. However, glyburide has a protein binding of 99.8%, compared to 96% percent for tolbutamide, for example. This means that only 0.2% of circulating glyburide is free to cross the placenta, compared to 4.0% of circulating tolbutamide. This degree of binding constitutes a 20-fold difference in the number of molecules available to cross the placenta. Interestingly, protein binding of glyburide is stable at serum concentrations exceeding 10-fold levels encountered during clinical use. The unique feature of glyburide is that its very high plasma protein binding is coupled with a short elimination half-life, due to both low volume of distribution (0.2 l/kg) and rapid clearance rate (1.3 ± 0.5 ml/kg/min) [34].

According to Kraemer et al. [35] very low transfer across the human placenta could also reflect efflux of glyburide back to the maternal circulation. Their study, in which they used the term placentas from nondiabetic women to quantify placental transfer of glyburide, provided the first evidence of transplacental efflux against a concentration gradient of glyburide from the fetal to the maternal circulation in humans as well as the first evidence of active efflux of any drug used in human pregnancy. Unlike Elliott et al. [15], they have excluded albumin from the perfusion buffer. Using closed-circle experiments and introducing glyburide to both maternal and fetal circulations, they noted highly significant fetal-to-maternal transfer of the drug against concentration gradient. Verapamil as a potent P-glycoprotein (P-gP) inhibitor did not modify glyburide transport. Investigators have suggested that glyburide is actively effluxed by a transporter other than P-gP.

This research was continued by Gedeon et al. [20] who utilized cell lines overexpressing P-gP, the breast

cancer resistance protein (BRCP) and the human multidrug resistance proteins (MRP1, MRP2, MRP3) in the presence or absence of specific inhibitors (verapamil, novobiocin and indomethacin, respectively) and examined potential involvement of these placental transporters in glyburide efflux. Their results clearly indicated that glyburide was preferentially transported by BRCP and MRP3 and these transporters might play a role in its distribution. Furthermore, glyburide was found to be an inhibitor of BRCP, P-gP, MRP1, MRP2 and MRP3 (Fig. 1).

The role of efflux transporters is unclear according to Nanovskaya et al. [42]. They questioned how BRCP or MRP3 could account for the difference in the higher net transfer of glyburide across the human placenta and concentrated on the effect of human serum albumin (HSA). Utilizing the technique of dual perfusion of the placental lobule in both open-open and closed-closed configuration, investigators noticed that the effect of HSA on glyburide transfer and its retention by the tissue was concentration-dependent and biphasic. The most evident effect of HSA was observed in its concentration range between 42–630 μg/ml (molar ratio for glyburide: HSA of 1:2–1:30). The concentration of 2.1 mg/ml HSA (glyburide: HSA molar ratio of 1:100) did not significantly affect the amount of drug retained by the tissue. The transfer rate of free/unbound glyburide to the fetal circuit was 73 ± 10% of the freely diffusible marker compound antipyrine. The authors concluded that the presence of HSA added in this test and released tissue proteins, which may also include albumin, in the maternal circuit are the major factors limiting the transplacental transfer of glyburide to the fetal circulation. Moreover, the binding of this drug to HSA reaches its maximum at a concentration of albumin significantly below that observed in pregnant women. In their opinion, the decrease in albumin concentration associated with pregnancy is unlikely to affect the disposition of glyburide [42].

The recirculating single-cotyledon human placental model that was employed in these studies is widely accepted to characterize the transport and metabolism of numerous drugs. It has been recognized as a safe *in vitro* surrogate for human placental transfer and is a practical model because it facilitates the study of intact human placenta independent of fetal metabolism. On the other hand, this model has its limitations. It is not clear how it represents earlier trimesters, especially in case of GDM. We also do not know how these results can be extrapolated to *in vivo* placental pharmacokinetics of glyburide.

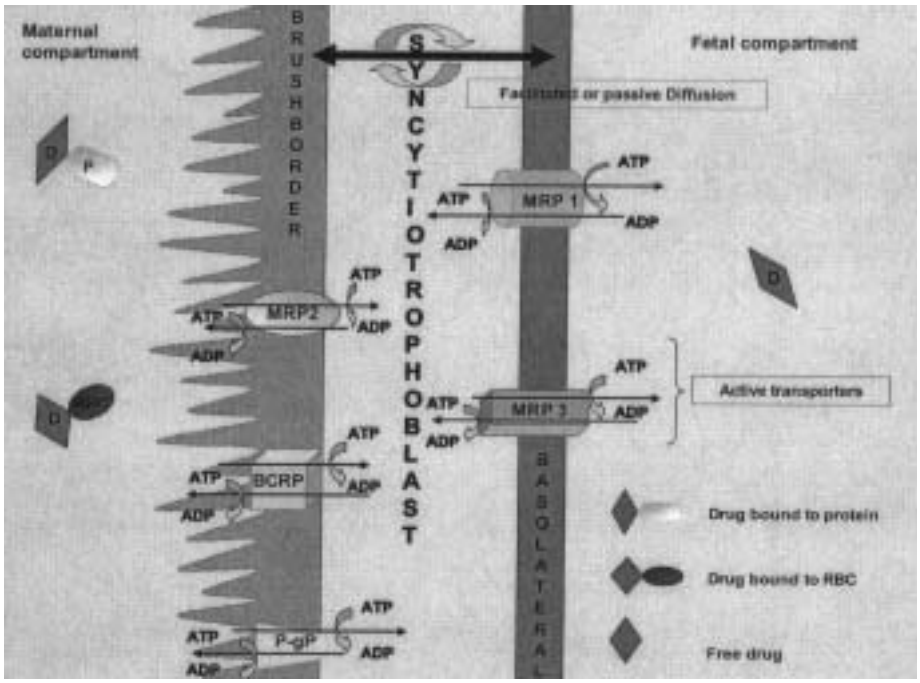

Fig. 1. Transport across the placental barrier; ADP – adenosine 5'-diphosphate, ATP – adenosine 5'-triphosphate, BRCP – breast cancer resistance protein, D – drug, MRP – human multidrug resistance protein, P – protein, P-gP – P-glycoprotein, RBC – red blood cell

In contrast to these studies, Sivan et al. [58] who examined placental transport of glyburide *in vivo* indicated that the drug crossed the placenta of pregnant rats. In that study, tritium-labeled glyburide, C^{14} albumin or C^{14}-labelled diazepam was injected into pregnant rats and the radioactivity was measured thereafter in maternal blood and in fetal extracts only. The ratios between radioactivities in fetal tissue to that in maternal blood for glyburide were similar to those of diazepam, which readily crosses the placenta but differed significantly from those for albumin, which does not cross. Moreover, glyburide in fetal tissue consistently reflected its concentration in maternal blood when measured at consecutive intervals after intravenous injection to the mother. In contrast, albumin in fetal tissue was low at all time points regardless of its levels in maternal blood when measured at different times after injection. However, these findings may be due to differences in placental permeability among species.

Transfer into breast milk

Earlier studies with two first-generation sulfonylureas, tolbutamide and chlorpropamide showed that there was a significant transfer of these drugs into breast milk. In a recent small nonrandomized controlled study, the use of second-generation sulfonylureas, glyburide as well as glipizide, was examined in lactation [16]. Both drugs appeared to be compatible with breast-feeding. Women were given either a single dose of glyburide (5 or 10 mg; n = 8) or a daily dose of glyburide or glipizide (5 mg/day; n = 5). No glyburide was found in milk samples, and the mean maximum theoretical infant dose as a percent of the weight-adjusted maternal dose was less than 1.5%, much lower than the usual acceptable threshold of 10%. Blood glucose levels were normal in all 3 infants who were wholly breast-fed [16].

Clinical studies

One of the first clinical studies that focused on glyburide therapy during pregnancy is research of Coetzee and Jackson [8]. These authors reported on the use of glyburide (combined with metformin) in pregnant women diagnosed with GDM and type 2 diabetes. They managed over 600 women between 1974 and 1983, and found decreased perinatal morbidity compared with the control group and no cases of serious neonatal hypoglycemia.

Since 2000 several studies have confirmed the observation that glyburide does not appear to adversely affect the fetus [6, 28, 36]. Nevertheless, the drug was used during the second trimester of pregnancy. In clinical studies, glyburide therapy was usually started with an initial daily dose of 2.5 mg with the morning meal. If glycemic control goals were not met, as defined by the individual provider, the dose was increased by 2.5 mg initially and thereafter by 5 mg weekly. If the dose exceeded 10 mg daily, twice daily dosing was considered. If glycemic goals were not met, as defined by the individual provider, on a maximum daily dose of 20 mg, patients were switched to insulin. Success in achieving the desired level of glycemia varied between the researches because of different doses and administration algorithm, length of therapy, type of patient (severity and ethnicity) and comparable groups (compliant and noncompliant subjects).

Langer et al. [39] compared glyburide with standard insulin therapy in a large randomized controlled trial in 404 women with GDM. In this study, 201 patients who were assigned to once-daily oral glyburide (2.5–20 mg/day; mean 9 mg/day) achieved blood glucose control on a par with that of 203 women assigned to subcutaneous injections of human insulin three times daily. The study did not address congenital malformations because subjects were recruited between 11 and 33 weeks of gestation, well after organogenesis. The rates of anomalies were similar in both groups and similar to previously reported rates of congenital anomalies in infants born to women without GDM.

In that study [39], the insulin- and glyburide-treated patients achieved comparable results in many variables: cesarean delivery, preeclampsia, cord-serum insulin concentrations, neonatal birth weight, macrosomia, neonatal metabolic complications (hypoglycemia, hypocalcemia, polycythemia and hyperbilirubinemia), respiratory complications and admission to the neonatal intensive care unit (NICU). Authors found that glyburide was as effective as insulin for the treatment of GDM, despite severity of disease when fasting plasma glucose in the glucose tolerance test was be-

tween 95 and 139 mg/dl. In that study, 82% of glyburide- and 88% of the insulin-treated patients achieved the desired level of glycemic control. In the study, only eight women (4%) initially assigned to glyburide needed to switch to insulin to attain mean blood glucose levels of 90–105 mg/dl.

Although maternal hypoglycemia is a well-known side effect of sulfonylurea drugs, in that study, an adequate glycemic control was obtained with significantly fewer hypoglycemic episodes in the glyburide group. Four women using glyburide had blood glucose measurements below 40 mg/dl, compared with 41 women using insulin. Concluding, of the maternal outcome variables assessed, none were significantly different between groups except the spectacular reduction ($p = 0.03$) in maternal hypoglycemic episodes in the glyburide-treated group (2%) compared with the 20% rate for insulin (Tab. 1).

Similar results pertained to maternal hypoglycemia were obtained by Yogev et al. [63]. Using a continuous glucose monitoring system that recorded data every 5 min for 72 consecutive hours with 288 measurements per day, asymptomatic hypoglycemic events (> 30 consecutive minutes of glucose values < 50 mg/dl) were identified in 19 of 30 (63%) insulin-treated patients and in 7 of 25 (28%) women treated with glyburide ($p = 0.009$). The mean recorded hypoglycemic episodes per day was significantly higher in insulin-treated patients than in patients treated with glyburide ($p = 0.03$). The majority of the hypoglycemic events were nocturnal (84%) in the insulin group, whereas in glyburide-treated patients these episodes were identified equally by day and night. Because there is a close relationship between maternal and fetal glucose concentrations during both early and late gestation, maternal hypoglycemia during pregnancy will, therefore, not only affect mother but may also affect the fetus [63]. It has been suggested that relative maternal hypoglycemia is associated with growth restriction in human studies [32, 40, 59]. Insulin-induced hypoglycemia in the last trimester of diabetic pregnancy has been shown to increase fetal body movement, decrease the fetal heart rate variability, increase the frequency and amplitude of fetal heart rate accelerations, and cause a slight decrease in the pulsatility index of the umbilical artery and an increase in the maternal catecholamine levels [4]. However, others have demonstrated that fetal well-being remains unaltered despite short-time moderate maternal hypoglycemia [48].

In contrast to these results are the findings of Bertini et al. [3], who demonstrated higher rates of neonatal hypoglycemia in the glyburide group as compared to insulin as well as acarbose group ($p = 0.006$). A higher rate of macrosomia (16%) and large for gestational age (25%) was found in the neonatal glyburide group compared with the acarbose (0 and 10.5%, respectively) and insulin groups (0 and 3.7%), while two cases of small for gestational age newborns were only observed in the group treated with insulin (7.4%). Nevertheless, in consideration of the fact that this randomized controlled trial was very small (< 30 subjects per group), results related to birth weight were not statistically significant. In that study, there was also no difference noticed in maternal glycemic control or cesarean section (Tab. 1).

In 2005 Langer et al. [41] further analyzed the association between glyburide dose, GDM severity, and selected maternal and neonatal factors. They found that glyburide dose increased with GDM severity. The success rate (i.e., achievement of glycemic control) decreased as disease severity increased. However, there was no difference between glyburide- and insulin-treated patients at each level of severity. Thus, achieving glycemic control – not the mode of pharmacological therapy – is the key to improving pregnancy outcome in GDM.

Jacobson et al. [28] performed a retrospective cohort study, in which the insulin group consisted of 268 subjects, and 236 were in the glyburide group. They found that women in the glyburide group had significantly lower post-treatment fasting ($p = 0.001$) and postprandial ($p = 0.001$) blood glucose levels. Nevertheless, maternal hypoglycemia, though rare, was more common in the glyburide group ($p < 0.001$). The failure rate with glyburide (necessitating a switch to insulin therapy) was 12% and was higher than that found by Langer et al. [39] (Tab. 1).

Moreover, Jacobson et al. [28] observed that women in the glyburide group had a higher incidence of preeclampsia even after controlling for confounders such as body mass index and ethnicity ($p = 0.02$; Tab. 1). This association has not been described in other studies, including prospective, randomized controlled trial of Langer et al. [39]. Furthermore, study of Jacobson et al. [28] did not have adequate statistical power to convincingly examine rare outcomes. On the other hand, it has been recognized that pregnancies complicated by GDM are associated with higher incidences of preeclampsia compared to women without

a diagnosis of GDM [43]. Although metformin, a biguanide, has been associated with increased risk of preeclampsia, this has not been noted with the sulfonylureas [27]. Animal studies suggest that glyburide inhibits vascular smooth muscle ATP-sensitive potassium channel activity and increases systemic

Tab. 1. Studies comparing efficacy of glyburide and insulin in the treatment of gestational diabetes mellitus

	Langer et al. [39]	Bertini et al. [3]	Jacobson et al. [28]	Ramos et al. [46]
Study design	RCT	RCT	Retro	Retro
Glyburide group (n)	201	24	236	78
Insulin group (n)	203	27	268	44
Glyburide failure	4%	20.8%	12%	16%
Maternal hypoglycemia (G *vs.* I)	p = 0.03 2 *vs.* 20	NS	p < 0.001 0.2 *vs.* 0.08	NS
Preeclampsia (G *vs.* I)	NS	NR	p = 0.02 6 *vs.* 12	NS
Cesarean delivery (G *vs.* I)	NS	NS	NS	NS
Macrosomia (G *vs.* I)	NS	NS	NS	NS
Neonatal hypoglycemia (G *vs.* I)	NS	p = 0.006 33.3 *vs.* 3.7	NS	p = 0.01 34 *vs.* 14
Phototherapy (G *vs.* I)	NS	NR	p = 0.046 9 *vs.* 5	NR
Admission to NICU (G *vs.* I)	NS	NR	p = 0.008 15 *vs.* 24	NR
Length of stay in NICU (G *vs.* I)	NR	NR	p = 0.002 8 *vs.* 4.3	NR

G *vs.* I – the frequency (expressed in per cent) or the duration (expressed in days) of a given parameter in patients treated with glyburide (G) and insulin (I), respectively; NICU – neonatal intensive care unit; NR – not reported; NS – no significant difference; RCT – randomized controlled trial; Retro – retrospective study

Tab. 2. Studies comparing glyburide success and its failure in the treatment of gestational diabetes mellitus

	Chmait et al. [6]	Conway et al. [9]	Rochon et al. [51]	Kahn et al. [30]
Study design	Prosp Obser	Prosp Obser	Prosp Obser	Prosp Obser
Glyburide success (n)	56	63	80	77
Glyburide failure (n)	13	12	21	18
FBG (S vs. F)	p < 0.001 101 *vs.* 126	p = 0.02 102 *vs.* 115	NS	p = 0.045 100 *vs.* 112
Cesarean delivery (S *vs.* F)	NS	NR	NS	NR
Macrosomia (S *vs.* F)	NS	NS	NS	NR
Neonatal hypoglycemia (S *vs.* F)	NS	NS	NS	NR
Admission to NICU (S *vs.* F)	NR	NR	NS	NR
Length of stay in NICU	NR	NR	NS	NR

FBG – fasting blood glucose; NICU – neonatal intensive care unit; NR – not reported; NS – no significant difference; Obser – observational study; Prosp – prospective study; S *vs.* F – the frequency (expressed in per cent) or the mean value (expressed in mg/dl) of a given parameter in the glyburide success (S) and failure groups (F), respectively

vascular resistance, and human *in vitro* studies report that glyburide antagonizes cicletanine-induced relaxation in arteries from women with preeclampsia and, therefore, may affect the natural vasodilatory substances of pregnancy [13, 31].

In the cited study of Jacobson et al. [28], neonates in the glyburide group were more likely to receive phototherapy ($p = 0.046$) and less likely to be admitted to the NICU ($p = 0.008$) though they had a longer NICU length of stay ($p = 0.002$; Tab. 1). This is in contrast to the findings of Rochon et al. [51], who showed increased rates of NICU admission in patients successfully managed with glyburide as compared with those women that were switched to insulin ($p = 0.037$) as well as there was no statistical difference in length of stay (Tab. 2).

Ramos et al. [46] retrospectively compared the effectiveness of glyburide and insulin for the treatment of GDM in women who had oral glucose challenge test ≥ 200 mg/dl and pretreatment fasting plasma glucose ≥ 105 mg/dl. In this study, 78 women were treated with insulin and 44 received glyburide. Seven women (16%) failed to achieve glycemic control on glyburide. There were no significant differences in birth weight, macrosomia, preeclampsia or cesarean delivery. Neonates in the glyburide group were diagnosed more frequently with hypoglycemia ($p = 0.01$; Tab. 1).

Kremer and Duff [36] reported the outcomes in a cohort of 73 women with GDM treated with glyburide. In this study, 81% had acceptable glucose control on medical therapy and 19% had to switch to insulin. Of those who responded to medication, 90% were successfully controlled with glyburide daily doses of 7.5 mg or less. Maternal side effects of therapy were relatively minor and led to discontinuation of medication in only one patient. Despite apparent effective glucose control, however, 19% of patients delivered macrosomic infants. The rates of NICU admission and neonatal morbidities were not reported [36].

Chmait et al. [6], in whose study women clearly preferred glyburide therapy over insulin, developed the following criteria that could be helpful in predicting glyburide therapeutic success in women with GDM: dietary failure after 30 weeks, or pretreatment fasting blood glucose levels < 110 mg/dl and 1-h postprandial values < 140 mg/dl on a antidiabetic diet. Authors studied 69 patients with GDM in whom dietary therapy failed and were then treated with glyburide (Tab. 2). Treatment failure was defined as inadequate glycemic control on 10 mg of glyburide twice daily. The glyburide failure rate was 18.8%. This study was conducted in a predominantly (87%) Hispanic population.

Similar results were obtained in a small cohort study of 75 patients with GDM in Texas, which suggested that a fasting glucose level of ≥ 110 mg/dl was associated with higher glyburide failure rates [9]. Kahn et al. [30] concluded that glyburide therapy was more likely to fail in women diagnosed earlier in pregnancy, of older age and multiparous, and with a higher mean fasting blood glucose, indicating that earlier glucose intolerance and a reduced capacity to respond to an insulin secretagogue may distinguish this group. However, according to Rochon et al. [51] only higher mean glucose values in the glucose challenge test ≥ 200 mg/dl were predictive of failure (Tab. 2).

Conclusions

Considering transplacental efflux against a concentration gradient from the fetal to the maternal circulation, glyburide seems to be the first generation drug on the path towards synthesizing an ideal drug specifically designed for pregnancy.

Since 2000, some studies have proven that glyburide is an effective alternative to insulin for achieving adequate glycemic control in women with GDM. When comparing different estimations of the success rate in achieving glycemic control, it should be noted that different criteria of successful glycemic control could influence study results. Furthermore, different populations (in terms of ethnicity and geographical location), sample size, quality and glucose testing method (self-monitoring; postprandial, preprandial or mean blood glucose) and the drug dosage (doses and algorithms) could also significantly affect the failure rate.

Echoing what ACOG stated in 2001, more intensive investigations are needed to evaluate the efficacy of glyburide as a treatment for pregnancies complicated by GDM. Until that time, we believe that insulin should be considered the first-line medical treatment of diabetes in pregnancy.

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