

Oral Antidiabetic Agents in Pregnancy and Lactation: A Paradigm Shift?

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Abstract and Introduction

Abstract

Objective: To provide information on the use of oral antidiabetic agents in pregnancy and breast-feeding.

Data Sources: Primary articles were identified by a MEDLINE search (1966-March 2007) using the MeSH headings: pregnancy in diabetics, pregnancy, polycystic ovary syndrome, hypoglycemic agents, glipizide, glyburide, metformin, rosiglitazone, pioglitazone, clinical trial, controlled clinical trial, multicenter study, randomized controlled trial, case-control studies, and cohort studies.

Study Selection and Data Extraction: All studies using oral antidiabetic agents in pregnancy were evaluated and relevant data were included in the discussion.

Data Synthesis: Studies of glyburide and glipizide have found little or no transfer of these drugs across the placenta, whereas metformin and rosiglitazone cross readily. Animal studies have found no evidence to suggest that glyburide, glipizide, metformin, or rosiglitazone are teratogenic. In gestational diabetes, glyburide was safe and efficacious; however, 16-19% of women failed to achieve optimal glucose control. No developmental toxicity in infants was observed when metformin was used before and throughout pregnancy in women with polycystic ovarian syndrome (PCOS). Some of the studies involving patients with type 2 diabetes had methodological problems. A randomized controlled trial using metformin for gestational diabetes in the third trimester is underway. The human information is inadequate to evaluate the risk of glipizide or the thiazolidinediones in pregnancy. In breast milk, 3 studies measured nonsignificant amounts of metformin and one study was unable to detect either glyburide or glipizide.

Conclusions: Neither glyburide nor metformin has caused developmental toxicity in humans. Glyburide has been used for the treatment of gestational diabetes, and metformin has been used in women with PCOS who eventually became pregnant. Additional trials are needed to better define the benefits and risks of oral antidiabetic agents in pregnancy. Metformin, glyburide, and glipizide appear to be compatible with breast-feeding.

Introduction

Insulin has long been the mainstay of treatment for women with gestational diabetes and type 2 diabetes in pregnancy. Although oral antidiabetic agents (OAAs) were used in these patients in the 1970s and 1980s, concerns arose from some studies that found increased rates of perinatal mortality and neonatal hypoglycemia.^[1-6] Because of these concerns, the use of OAAs in pregnancy was strongly discouraged. However, more recent data on oral agents in women with gestational diabetes and polycystic ovarian syndrome (PCOS) suggest that an important paradigm shift is occurring regarding their use in pregnancy.

The objective of this review was to examine the recent evidence regarding the safety of oral agents in pregnancy and lactation, including their transfer across the placenta or into breast milk, possible teratogenicity, and potential developmental consequences of drug exposure.

Do All Oral Antidiabetic Agents Cross the Placenta?

The basis for the long-standing apprehension for use of OAAs during pregnancy stems from the assumption that these drugs cross the placenta.^[7] It has been hypothesized that placental transfer results in stimulation of the fetal pancreas and subsequent fetal/neonatal hypoglycemia.^[4-6] However, during the past decade, it has become evident that not all OAAs cross the placenta equally, and some do not cross at all.

Sulfonylureas

Sulfonylureas act by increasing insulin secretion from the pancreas. They bind to the sulfonylurea receptor on the pancreatic β cells, leading to inhibition of the potassium channel and reduction of the resting membrane potential.^[8] This leads to the opening of the calcium channel and an increase in intracellular calcium, resulting in the release of insulin from secretory granules. Elliot et al.^[7] tested 4 sulfonylureas for placental transfer using the human placental cotyledon perfusion model. This model replicates the in vivo situation more closely than do subcellular or cell culture systems, obviating the need for human in vivo studies and avoiding the inappropriate use of animal models.^[9] The investigators found that, while the first-generation sulfonylureas crossed the placenta readily (21.5% for tolbutamide, 11% for chlorpropamide), the second-generation sulfonylureas crossed to a much lesser extent (glipizide 6.6%).^[7] In particular, a small percentage (3.9%) of glyburide (glibenclamide) crossed.

Further evidence that glyburide does not cross the placenta came from a study in which serum and cord blood glyburide levels were measured in 12 pregnant women who were taking glyburide (mean dose 9 mg/day, maximum 20 mg/day).^[10] While glyburide was measurable in the serum of these women, none was detected in the cord blood. Possible reasons for the minimal transfer of glyburide include its high protein binding (99.8%) and short elimination half-life (10 h). Another possibility is that the placenta is actively pumping glyburide back into the maternal circulation by adenosine-triphosphate-binding cassette transporters, most notably breast cancer-related protein and multiple resistance protein 3.^[11]

Biguanides

Biguanides (metformin) work to lower blood glucose levels primarily by decreasing hepatic gluconeogenesis.^[12] Other mechanisms of action include increased peripheral glucose disposal and reduced intestinal glucose absorption. Metformin has been shown to pass freely across the placenta.^[13] Two in vivo studies measured maternal and cord blood samples in women taking metformin throughout pregnancy (850 mg twice daily in 15 women^[13] and 2000 mg/day in 8 women^[14]). The results of these trials showed that the fetus is exposed to concentrations as high or higher than those seen in the mother.

Thiazolidinediones

Thiazolidinediones (rosiglitazone, pioglitazone) act as high-affinity ligands of the peroxisome proliferator-activated receptor- γ receptor (PPAR- γ), a nuclear transcription factor.^[15] Once activated, PPAR- γ binds to specific DNA binding sites called PPAR-responsive elements, leading to changes in gene expression that improve insulin sensitivity in adipose tissue, muscle, and the liver. In a recent in vivo study looking at rosiglitazone placental transfer, 31 women who were undergoing surgical terminations at 8-12 weeks of gestation were given two 4 mg doses of rosiglitazone.^[16] Analysis of fetal tissue, coelomic fluid, and amniotic fluid revealed that rosiglitazone crossed the placenta in all women, especially in those over 10 weeks' gestation. There have been no third-trimester studies or in vitro placental cotyledon transfer studies published to date.

Summary

Well-designed studies using the in vitro human placental cotyledon model, as well as in vivo studies, have demonstrated that while metformin, rosiglitazone, and most sulfonylureas cross the placenta, glyburide has been shown to cross very little.

Oral Antidiabetic Agents in the First Trimester: Are They Teratogenic?

Animal Data

Data from studies in rats and rabbits revealed that neither glyburide nor glipizide was teratogenic, even when given in large doses.^[17] In rats that were fed doses of metformin 4 times the maximum recommended human dose (MRHD), less than 0.5% of rat fetuses developed ocular and central nervous system malformations. Studies using rosiglitazone in rats and rabbits did not find the drug to be teratogenic at exposures 20-75 times that obtained with the MRHD, although pioglitazone did show increased postimplantation losses at doses 10-40 times the MRHD.^[18]

Human Data

In cohort studies of women with type 2 diabetes taking either sulfonylureas (when specified: glyburide 5-20 mg/day), biguanides (metformin 1.5-3 g/day), or both,^[1-3,19-23] only 2 studies showed an increased rate of congenital anomalies in women taking oral agents compared with women taking insulin.^[21,22] These studies were small (20 and 43,

respectively); women did not have ideal glycemic control (hemoglobin A_{1C} in exposed mothers was 8.8%,^[21] and not reported^[22]); and a regression analysis was not performed in either study to control for glycemic control.^[21,22] In a meta-analysis evaluating the safety of oral agents (sulfonylureas and biguanides) administered in the first trimester, 10 studies on 471 exposed women were included.^[24] No significant difference was found in the rate of major malformations or neonatal death among women with first-trimester exposure to oral antidiabetic agents compared with nonexposed women. One of the limitations of this meta-analysis was that studies were heterogeneous.

In a well-designed study that controlled for glycemic control in 147 women exposed to sulfonylureas (chlorpropamide, glyburide, or glipizide; doses not specified), there was no association between anomalies and use of oral agents.^[20] However, maternal glycohemoglobin was independently associated with congenital anomalies, suggesting that hyperglycemia, rather than the use of oral agents, is important in the etiology of these congenital anomalies. Limited information is available regarding the use of thiazolidinediones in pregnancy. A case report described one patient with type 2 diabetes who was exposed to rosiglitazone 4 mg/day in the first 7 weeks of gestation and then delivered a healthy infant.^[25]

We can learn about the safety of metformin and thiazolidinediones from studies in women with PCOS. An increasing number of women with PCOS are using insulin sensitizers to improve ovulation rates. Unlike women with type 2 diabetes, these women do not have increased glucose levels, which may serve as a confounding factor when investigating congenital anomalies and perinatal mortality. A Cochrane review showed that metformin, when used alone, increases ovulation rates by a factor of 3.9 and pregnancy rates by a factor of 3.3.^[26] When metformin is used in combination with clomiphene citrate, ovulation and pregnancy rates are even higher. In several studies (case series, cohort studies, 1 randomized controlled trial) in more than 500 women using metformin in the first trimester (0.5-2.55 g/day) or throughout pregnancy (1-2.55 g/day), metformin did not lead to an increased incidence of anomalies in women with PCOS.^[13,27-33] Thiazolidinediones have also been shown to stimulate spontaneous and clomiphene-induced ovulation.^[34,35] A case report described one patient with PCOS who took rosiglitazone 4 mg/day for the first 4 weeks of the pregnancy and delivered a healthy infant.^[36]

In summary, from animal and human data, it appears that sulfonylureas and biguanides confer a low risk for teratogenicity. More data are needed before conclusions can be made regarding the teratogenicity of thiazolidinediones.

Use of Oral Antidiabetic Agents in the Second and Third Trimesters

Glyburide

Langer et al.^[10] conducted a large randomized controlled trial of glyburide 2.5-20 mg/day (mean 9) compared with insulin in 404 women with gestational diabetes. No significant difference was found in glycemic control or neonatal outcomes, which included birth

weight, large size for gestational age (LGA), macrosomia, hypoglycemia, hypocalcemia, hyperbilirubinemia, polycythemia, lung complications, admission to neonatal intensive care unit, congenital anomalies, and perinatal mortality. In this study, the 95% CI for the absolute risk reduction in LGA was -7.8% to 6.0%, meaning that it is unlikely that the glyburide group had an LGA rate more than 6% higher than the rate of the insulin group, a small difference. In a smaller randomized controlled trial (N = 70) of glyburide, insulin, or acarbose, again there was no difference noted in glycemic control or birth weight, although this study lacked the power for these outcomes.^[37] Significantly more neonates in the glyburide group had hypoglycemia (33.3% vs 3.7%; p = 0.006); however, this study was very small (<30 per group).

A relatively large retrospective cohort study (N = 578) comparing glyburide 2.5-20 mg/day and insulin use in 2 time periods also failed to show significant differences in glycemic control, macrosomia, C-section, and neonatal hypoglycemia, although the investigators did find significantly higher incidences of preeclampsia (12% vs 6%; p = 0.02) and phototherapy rates (9% vs 5%; p = 0.046) in the glyburide group.^[38] While no explanation was given for the increased phototherapy rates, with regard to preeclampsia, the authors discussed one animal study and one human in vitro study suggesting a possible link between glyburide and increased vascular resistance. This association has not been described in other studies and was not found in a prospective, randomized controlled trial.^[10]

More than 800 women have reportedly used glyburide in pregnancy.^[10,38-42] Approximately 16-19% of women given glyburide for gestational diabetes failed to achieve optimal glycemic control and needed to be switched to insulin. Failure is predicted if fasting glucose levels are greater than 110 mg/100 mL, diagnosis is made before 25 weeks' gestation, and glucose levels are high on the oral glucose tolerance test.^[41,42] Despite this, glyburide's popularity as first-line therapy for the treatment of gestational diabetes appears to be growing. Although the drug has not been approved for use in pregnancy by the American Diabetes Association^[43] or American College of Obstetrics and Gynecology (ACOG),^[44] in a survey of ACOG Fellows, 13% stated that they use glyburide as first-line therapy for the treatment of gestational diabetes.^[45] Such treatment was very uncommon just 5 years ago (authors' observation).

There are no data on the use of glipizide in pregnancy.

Metformin

Observational studies using metformin (1.5-3 g/day) in pregnant women with type 2 diabetes have been fraught with problems.^[1-3,21] Studies have been small (N = 1-33), and glycemic control tended to be poor, accounting for high perinatal mortality.^[1,3,21] The incidence of perinatal mortality decreased when glycemic control improved after 1977.^[1-3] In one study, use of metformin 1.5-2.5 g/day was associated with a significantly increased rate of preeclampsia (32% vs 10% using insulin; p < 0.001) and perinatal mortality (11.6 vs 1.3%; p < 0.02).^[23] These patients, however, were more obese than were those taking insulin, a probable confounding factor. The perinatal mortalities were unlikely related to metformin therapy. Two women who had stillbirths had poor glycemic

control, and 2 others who were obese had polyhydramnios and preeclampsia. The woman with preeclampsia had taken metformin from 36 weeks' gestation. Another mother whose infant died of congenital anomalies had taken metformin only in the second trimester.

Several cohort studies of women with PCOS using metformin 1.5-2.55 g/day throughout pregnancy have illustrated the relative safety of the drug in the second and third trimesters.^[13,27,30-33,46] These studies found decreased rates of spontaneous abortion and gestational diabetes and similar rates of preeclampsia, major birth defects, and similar birth weight compared with healthy controls.^[27,30-33,46] These data are encouraging, but most of these studies were small (<75 per group) and retrospective. In a somewhat larger (N = 90) prospective study of women with PCOS who were taking metformin (the majority throughout the pregnancy), there was no increased rate of perinatal mortality or preeclampsia when compared with 252 healthy controls.^[31] Height, weight, and motor and social development were also normal in the infants at 3 and 6 months. Data are needed from randomized controlled trials to confirm these findings.

Most women with diabetes in pregnancy require increasing doses of insulin for good glycemic control; some women with exceptionally high insulin resistance require very large doses of insulin for optimal control. It has been hypothesized that metformin may help to sensitize these women to insulin, thus allowing for lower amounts of insulin to be used.^[47] The safety of this approach, however, has yet to be demonstrated.

Investigators in New Zealand are conducting the Metformin in Gestational Diabetes (MiG), a randomized controlled trial evaluating metformin treatment compared with insulin in 750 women with gestational diabetes.^[48] The investigators hypothesize that, in women receiving metformin, insulin sensitivity will be improved for both mother and fetus. These investigators plan to follow the offspring and evaluate later insulin sensitivity (with bloodwork at 5-6 y) and health (at 2 y and onward) by assessment of diet, activity, neurodevelopment, physical examination, and body composition.

Thiazolidinediones

Few data are available regarding thiazolidinedione use in the second and third trimesters of pregnancy. One case report described a patient who was exposed to rosiglitazone 4 mg/day in the second trimester (weeks 13-17) and delivered a healthy infant.^[49]

Summary

Evidence has shown that glyburide may be a reasonable alternative to insulin for some women with gestational diabetes, especially those who have fasting glucose concentrations less than 110 mg/100 mL and are in the third trimester. Data are lacking regarding the use of glipizide in pregnancy. Randomized controlled trial data are needed to assess the efficacy and safety of metformin use in women with gestational diabetes (in progress), and throughout pregnancy in women with PCOS. The use of metformin in women with type 2 diabetes in pregnancy to reduce insulin levels needs further

investigation.

Long-term Outcomes

Little is known about the long-term outcomes of the use of OAAs in pregnancy. One recent study examining the use of metformin throughout pregnancy in 109 women with PCOS found normal growth and motor development in infants (126 live births) followed up to 18 months.^[50]

Use of Oral Antidiabetic Agents in Breast-Feeding

With the increasing incidence of type 2 diabetes in younger people, the incidence of women with type 2 diabetes in pregnancy is increasing.^[51,52] These women are often on OAAs prior to pregnancy, and while they are switched to insulin for pregnancy, they are often anxious to return to their oral agents postpartum. First-generation sulfonylureas, tolbutamide and chlorpropamide, have been found to cross into breast milk.^[18] In a recent nonrandomized controlled study, the use of second-generation sulfonylureas, glyburide and glipizide, was examined in lactation.^[53] 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%.^[54] Blood glucose levels were normal in all 3 infants who were wholly breast-fed.

To date, there have been 3 studies looking at the use of metformin with breast-feeding, and they suggest that metformin is excreted into breast milk at very low levels.^[55-57] Twenty-two women were given metformin while breast-feeding, either as a single dose (500 mg, n = 5), or for several days to weeks of use (1000-1500 mg/day, n = 17). The mean milk:plasma ratio was 0.35:0.63, and the mean estimated infant dose as a percentage of the mother's weight-adjusted dose was 0.18-0.65%.^[55-57] In 3 of 3 infants, blood glucose concentrations measured 4 hours after feeding were within normal limits.^[57] While these studies are reassuring, only one study has looked at long-term infant outcomes. In a comparison of 61 nursing infants with 50 formula-fed infants of mothers taking metformin throughout pregnancy and lactation, there was no significant difference in weight, height, or motor-social development at 3 and 6 months of age.^[58]

There have been no reports to date of studies evaluating the passage of thiazolidinediones into breast milk.

Summary

The available data suggest that glyburide and metformin are not teratogenic in humans when used in clinically recommended doses. The data also suggest that glyburide may be used for the treatment of gestational diabetes in some women, while metformin may be used safely for ovulation in women with PCOS. Metformin, glyburide, and glipizide appear to be compatible with breast-feeding. Randomized controlled trials will better

elucidate the benefit of glyburide, metformin, and thiazolidinediones in pregnancy and over the long-term.

Such data on the use of OAs in pregnancy are shifting the paradigm that once stated that they should never be used in pregnancy. This shift may be welcome to women with gestational diabetes who are inconvenienced by injections and to those in areas where insulin may not be readily available or is cost prohibitive. With the growing rates of diabetes, especially in the developing world, such a shift in paradigm may be greatly appreciated.

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