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## A COMPARISON OF GLYBURIDE AND INSULIN IN WOMEN WITH GESTATIONAL DIABETES MELLITUS

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### ABSTRACT

**Background** Women with gestational diabetes mellitus are rarely treated with a sulfonylurea drug, because of concern about teratogenicity and neonatal hypoglycemia. There is little information about the efficacy of these drugs in this group of women.

**Methods** We studied 404 women with singleton pregnancies and gestational diabetes that required treatment. The women were randomly assigned between 11 and 33 weeks of gestation to receive glyburide or insulin according to an intensified treatment protocol. The primary end point was achievement of the desired level of glycemic control. Secondary end points included maternal and neonatal complications.

**Results** The mean ( $\pm$ SD) pretreatment blood glucose concentration as measured at home for one week was  $114 \pm 19$  mg per deciliter ( $6.4 \pm 1.1$  mmol per liter) in the glyburide group and  $116 \pm 22$  mg per deciliter ( $6.5 \pm 1.2$  mmol per liter) in the insulin group ( $P=0.33$ ). The mean concentrations during treatment were  $105 \pm 16$  mg per deciliter ( $5.9 \pm 0.9$  mmol per liter) in the glyburide group and  $105 \pm 18$  mg per deciliter ( $5.9 \pm 1.0$  mmol per liter) in the insulin group ( $P=0.99$ ). Eight women in the glyburide group (4 percent) required insulin therapy. There were no significant differences between the glyburide and insulin groups in the percentage of infants who were large for gestational age (12 percent and 13 percent, respectively); who had macrosomia, defined as a birth weight of 4000 g or more (7 percent and 4 percent); who had lung complications (8 percent and 6 percent); who had hypoglycemia (9 percent and 6 percent); who were admitted to a neonatal intensive care unit (6 percent and 7 percent); or who had fetal anomalies (2 percent and 2 percent). The cord-serum insulin concentrations were similar in the two groups, and glyburide was not detected in the cord serum of any infant in the glyburide group.

**Conclusions** In women with gestational diabetes, glyburide is a clinically effective alternative to insulin therapy. (N Engl J Med 2000;343:1134-8.)

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**H**YPERGLYCEMIA is associated with adverse outcomes of pregnancy in women with gestational or preexisting diabetes mellitus. The principal approach to glycemic control in pregnant women with diabetes is dietary therapy, with the addition of insulin when diet alone is not sufficient.<sup>1-4</sup> Insulin therapy is effective in achieving the appropriate levels of glycemia, but it is inconvenient and expensive. An alternative approach would be attractive.

Several authoritative bodies<sup>2-4</sup> recommend that sulfonylurea drugs not be given during pregnancy because of their potential to cause neonatal hypoglycemia and fetal anomalies.<sup>5-11</sup> This recommendation is based mainly on studies done before the availability of drugs such as glyburide and glipizide, which are in common use today.<sup>12-28</sup> We have demonstrated in laboratory studies that glyburide does not cross the human placenta in appreciable quantities,<sup>29</sup> in contrast to older sulfonylurea drugs and metformin.<sup>30,31</sup> On the basis of these findings and the relatively mild hyperglycemia in most pregnant women with gestational diabetes, we hypothesized that glyburide might be an alternative to insulin therapy in such women.

### METHODS

#### Subjects

We studied 404 women with gestational diabetes who were being treated at maternal health clinics in San Antonio, Texas. Pregnant women attending these clinics were screened for diabetes with a one-hour, 50-g oral glucose challenge. Women who had plasma glucose concentrations above 130 mg per deciliter (7.3 mmol per liter) at one hour underwent a 100-g oral glucose-tolerance test.

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Women with two or more abnormal plasma glucose values were given a diagnosis of gestational diabetes.<sup>32</sup>

Eligibility for the study was limited to women with singleton pregnancies and gestational diabetes who had fasting plasma glucose concentrations on the day of oral glucose-tolerance testing of at least 95 mg per deciliter (5.3 mmol per liter) and less than 140 mg per deciliter (7.8 mmol per liter) and were at 11 to 33 weeks of gestation. Women with fasting plasma glucose concentrations of less than 95 mg per deciliter were initially treated with diet but were subsequently enrolled in the study if their fasting plasma glucose concentrations were at least 95 mg per deciliter or their postprandial plasma glucose concentrations were at least 120 mg per deciliter (6.7 mmol per liter). The study was approved by the institutional review board of the University of Texas Health Science Center at San Antonio. Written informed consent was obtained from the women.

The women were randomly assigned to receive glyburide or human insulin according to a computer-generated list, by means of sequentially numbered, opaque, sealed envelopes. At the initial visit, a detailed history was obtained that included demographic data, ethnic background (as reported by the women), social history, and a summary of past obstetrical and medical information. Women with a prepregnancy body-mass index (the weight in kilograms divided by the square of the height in meters) of 27.3 or more were considered obese.

#### Maternal Assessment and Treatment

All the women were provided with standard nutritional instructions for three meals and four snacks daily. Adherence to the dietary regimen was evaluated and reinforced at weekly visits to the clinic. The diets were designed to provide 25 kcal per kilogram of body weight for the obese women and 35 kcal per kilogram for the nonobese women, with 40 to 45 percent of the calories from carbohydrates.

In the women assigned to receive insulin, the starting dose was 0.7 unit per kilogram of actual body weight at admission, given subcutaneously three times daily and increased weekly as necessary.<sup>33-35</sup> In the women assigned to receive glyburide, the starting dose was 2.5 mg orally in the morning. When indicated, the dose of glyburide was increased the following week by 2.5 mg and thereafter by 5 mg weekly up to a total of 20 mg when necessary to achieve glycemic control.

A nurse educator instructed the women in how to measure blood glucose with a glucometer. They were asked to perform measurements seven times daily: after an overnight fast, before meals, two hours after meals, and at bedtime.<sup>36,37</sup> The patients began testing of blood glucose one week before the initiation of therapy. In addition, glycosylated hemoglobin and serum C peptide were measured during this time, and glycosylated hemoglobin testing was repeated late in the third trimester. For purposes of quality control, blood glucose was measured with the glucometer and simultaneously in the laboratory at each weekly clinic visit.

The primary outcome variable was achievement of the desired level of glycemic control. The goals of treatment were the achievement of a mean blood glucose concentration of 90 to 105 mg per deciliter (5.0 to 5.9 mmol per liter), a fasting blood glucose concentration of 60 to 90 mg per deciliter (3.4 to 5.0 mmol per liter), a preprandial blood glucose concentration of 80 to 95 mg per deciliter (4.5 to 5.3 mmol per liter), and a postprandial blood glucose concentration of less than 120 mg per deciliter (6.7 mmol per liter). At each visit, the care provider evaluated the blood glucose values and, when necessary, increased the dose of insulin or glyburide as needed to meet these goals. If the blood glucose values of a woman treated with the maximal dose of glyburide did not meet the goals for a two-week period, her treatment was switched to insulin therapy.

Antepartum care was provided by subspecialists in maternal and fetal medicine, residents, nurse educators, dietitians, and social workers according to the same treatment protocol for both groups, except for the assignment to insulin or glyburide. A standard proto-

col for the management of labor and delivery was used for both treatment groups. The antepartum, labor-and-delivery, and neonatal teams were aware of the patients' treatment-group assignments.

#### Fetal and Neonatal Assessment

Gestational age was determined on the basis of the menstrual history, in conjunction with an early vaginal examination. When ultrasonography was performed before 20 weeks of gestation, it was used to determine gestational age.

At delivery, all neonates were evaluated and followed by the neonatal team. Infants with birth weights at or above the 90th percentile were considered large for gestational age, and those with birth weights at or below the 10th percentile were considered small for gestational age, on the basis of growth standards derived from the San Antonio population.<sup>38</sup> Macrosomia was defined as a birth weight of 4000 g or more. Neonatal respiratory outcomes included the presence or absence of hyaline membrane disease and transient tachypnea (defined as respiratory distress in infants born near term that lasted for about three days). The diagnosis of hyaline membrane disease was based on the criteria of Corbet et al.<sup>39</sup>

For each infant, insulin was measured in the cord serum and glucose in the heel blood at least three times during the first hour after birth, and then every 30 minutes up to hour 4. Hypoglycemia was defined as present when there were two consecutive blood glucose values of 40 mg per deciliter (2.2 mmol per liter) or less. Hyperbilirubinemia was defined as a serum bilirubin concentration of at least 12 mg per deciliter (205  $\mu$ mol per liter). Serum bilirubin was measured when there was clinical evidence of jaundice. The hematocrit was measured in cord blood from all infants, and polycythemia was defined as a hematocrit above 60 percent. Serum calcium was measured when clinically indicated; hypocalcemia was defined as a serum calcium concentration of 7.0 mg per deciliter (1.8 mmol per liter) or less.

#### Laboratory Analysis

Serum insulin was measured by a double-antibody radioimmunoassay. The sensitivity of the assay was 1  $\mu$ U per milliliter, and the intraassay and interassay coefficients of variation were 3.9 percent and 5.6 percent, respectively. There was no cross-reactivity with C peptide, and there was 18 percent cross-reactivity with proinsulin.<sup>40</sup> Serum C peptide was measured by radioimmunoassay. Glyburide was measured in the cord serum by high-performance liquid chromatography with ultraviolet detection. The limit of detection of this method was 10 ng per milliliter at a signal-to-noise ratio of 5.<sup>41,42</sup>

#### Statistical Analysis

Analysis was performed on the basis of the intention to treat. Chi-square tests were used to compare categorical data between the two treatment groups, and Student's t-tests to compare numerical data.

## RESULTS

#### Maternal Outcomes

Of the 404 women enrolled in the study, 201 were assigned to receive glyburide and 203 to receive insulin. The women ranged in age from 18 to 40 years and were all Medicaid recipients; the majority had completed the 10th grade. Approximately 83 percent were Hispanic, mostly Mexican American, 12 percent were non-Hispanic white, and 5 percent were black. The base-line characteristics of the two treatment groups were similar (Table 1).

One hundred thirty-nine women in the glyburide group (69 percent) and 146 women in the insulin group (72 percent) had fasting plasma glucose concentrations of at least 95 mg per deciliter at diagnosis. The daily blood glucose concentrations and gly-

**TABLE 1.** CHARACTERISTICS OF 404 WOMEN WITH GESTATIONAL DIABETES.\*

CHARACTERISTIC	GLYBURIDE (N=201)	INSULIN (N=203)
Age — yr	29±7	30±6
BMI ≥27.3 before pregnancy — no. (%)†	141 (70)	132 (65)
Nulliparity — no. (%)	56 (28)	59 (29)
Family history of diabetes — no. (%)	86 (43)	91 (45)
Previous gestational diabetes — no. (%)	24 (12)	22 (11)
Previous delivery of infant with macrosomia — no. (%)	36 (18)	45 (22)
Screening plasma glucose — mg/dl‡	169±28	169±31
Wk of gestation	24±7	25±7
Wk of gestation at delivery	38.7±1.6	38.5±2.1
Results of oral glucose-tolerance test — mg/dl‡		
Fasting	97±14	98±16
At 1 hr	197±31	201±30
At 2 hr	174±31	174±29
At 3 hr	140±37	134±37
Serum C peptide — ng/ml§	3.8±2.3	3.4±1.5
Dose of glyburide — mg/day	9±6	—
Dose of insulin — units/day¶	—	85±48
No. of clinic visits attended	11±5	12±6
No. of clinic visits missed	1.5±2.1	1.2±2.2
No. of measurements of blood glucose/day	4±2	4±2
Weight gain — lb	21±17	21±15

\*Plus-minus values are means ±SD. There were no significant differences between the two groups in any characteristics by the chi-square test or Student's t-test.

†The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.

‡Values shown are for plasma glucose. To convert values for glucose to millimoles per liter, multiply by 0.056.

§To convert values for C peptide to nanomoles per liter, multiply by 0.331.

¶Mean insulin doses were calculated from diagnosis to delivery.

||The mean values were calculated from the weight before pregnancy to the last weight measured within a week before delivery. To convert values for weight gain to kilograms, divide by 2.2.

cosylated hemoglobin values were similar in the two groups before and during treatment (Tables 2 and 3). The mean (±SD) plasma glucose concentration measured during clinic visits was 102±24 mg per deciliter (5.7±1.3 mmol per liter) in the glyburide group and 99±22 mg per deciliter (5.5±1.2 mmol per liter) in the insulin group. Furthermore, there was a strong association between these values and self-monitored blood glucose values at the same visit ( $r=0.96$ ,  $P<0.001$ ); 165 women in the glyburide group (82 percent) and 179 women in the insulin group (88 percent) had blood glucose values measured at home that fell into the desired ranges. In eight women in the glyburide group (4 percent), the maximal dose failed to produce good glycemic control, and these women were switched to insulin therapy.

Four women in the glyburide group and 41 women

**TABLE 2.** BLOOD GLUCOSE CONCENTRATIONS MEASURED AT HOME AND GLYCOSYLATED HEMOGLOBIN VALUES BEFORE TREATMENT IN WOMEN WITH GESTATIONAL DIABETES.\*

VARIABLE	GLYBURIDE (N=201)	INSULIN (N=203)	P VALUE†
Blood glucose (mg/dl)‡			
Fasting	104±25	108±26	0.12
Preprandial	104±20	107±23	0.16
Postprandial	130±25	129±27	0.69
Mean	114±19	116±22	0.33
Glycosylated hemoglobin (%)	5.7±1.3	5.6±1.2	0.42

\*Values are means ±SD.

†P values were calculated by a two-tailed t-test.

‡Blood glucose was measured at home during a one-week period. To convert values for glucose to millimoles per liter, multiply by 0.056.

in the insulin group had blood glucose concentrations below 40 mg per deciliter (2.2 mmol per liter) ( $P=0.03$ ). In none of the women were more than 6 percent of the measurements below this value. None of the women reported severe symptoms, such as confusion, poor coordination, double vision, headache, or combativeness, or an inability to treat their symptoms themselves. The incidence of preeclampsia and the rate of cesarean section were similar in the glyburide group and the insulin group (6 percent vs. 6 percent and 23 percent vs. 24 percent, respectively).

### Neonatal Outcomes

There were no significant differences between the two groups in perinatal outcome (Table 4). Stratification of the women into two groups according to their mean blood glucose concentrations measured at home (at least 106 mg per deciliter and no more than 105 mg per deciliter) did not uncover any differences in outcomes. Among the infants born to the women with the higher blood glucose concentrations, 17 percent in the glyburide group were large for gestational age, as were 19 percent in the insulin group; the incidence of macrosomia was 11 percent and 10 percent, respectively. Among the infants of the women with the lower blood glucose levels, 7 percent in the glyburide group and 10 percent in the insulin group were large for gestational age; the incidence of macrosomia was 4 percent and 3 percent, respectively.

Glyburide was not detected in the cord serum of any infant. The mean time from the last dose of glyburide to sampling of the cord blood was 8±4 hours. In 12 randomly selected women in the glyburide group, glyburide was measured at the same time in maternal and cord serum. The maternal serum glyburide concentrations ranged from 50 to 150 ng per milliliter, whereas glyburide was undetectable in cord serum. When the data were stratified according to whether the women entered the study at 11 to 20

**TABLE 3. BLOOD GLUCOSE CONCENTRATIONS MEASURED AT HOME AND GLYCOSYLATED HEMOGLOBIN VALUES DURING TREATMENT IN WOMEN WITH GESTATIONAL DIABETES.\***

VARIABLE	GLYBURIDE (N=201)	INSULIN (N=203)	P VALUE†
Week of gestation when blood glucose testing started	28±6	27±8	0.22
No. of weeks of testing	10±6	11±7	0.12
Blood glucose (mg/dl)‡			
Fasting	98±13	96±16	0.17
Preprandial	95±15	97±14	0.17
Postprandial	113±22	112±15	0.60
Mean	105±16	105±18	0.99
Glycosylated hemoglobin (%)§	5.5±0.7	5.4±0.6	0.12

\*Values are means ±SD.

†P values were calculated by a two-tailed t-test.

‡Blood glucose values are means of measurements obtained throughout pregnancy. To convert values for glucose to millimoles per liter, multiply by 0.056.

§The test was performed late in the third trimester.

weeks' gestation or after the 20th week of gestation, no differences were found between the treatment groups in neonatal outcomes; for example, the incidence of macrosomia in the glyburide and the insulin groups was 8 percent and 6 percent, and the proportion of infants who were large for gestational age was 12 percent and 13 percent, respectively. There were also no differences in the degree of glycemic control, the rate of cesarean section, or the rate of preeclampsia after stratification according to gestational age.

### DISCUSSION

We found that among women with gestational diabetes, the degree of glycemic control and the perinatal outcomes were essentially the same for those treated with glyburide and those treated with insulin. The lack of differences between the infants born to mothers in the two treatment groups corroborated the results in the mothers.

Infants may be large because they are large for gestational age or because they have macrosomia. This distinction is important, because early intervention for delivery may be a confounding factor in the proportion of infants who are large. The rate of delivery of large-for-gestational-age infants and the incidence of macrosomia in our study were similar to the rates reported in women without diabetes.<sup>1,43</sup> The primary action of sulfonylurea drugs is to increase insulin secretion,<sup>44,45</sup> thereby decreasing hepatic glucose production and leading to a reversal of glucose toxicity and indirect improvement of insulin sensitivity.<sup>46-48</sup> We found that glyburide was as effective as insulin in producing glycemic control, and few women assigned to glyburide had to be switched to insulin.

Glyburide was not detected in the cord serum of

**TABLE 4. NEONATAL OUTCOMES.\***

OUTCOME	GLYBURIDE (N=201)	INSULIN (N=203)	P VALUE
<b>Neonatal features</b>			
Large size for gestational age — no. (%)	24 (12)	26 (13)	0.76
Birth weight — g	3256±543	3194±598	0.28
Ponderal index >2.85 — no. (%)†	18 (9)	24 (12)	0.33
Macrosomia — no. (%)	14 (7)	9 (4)	0.26
<b>Metabolic outcomes</b>			
Cord-serum insulin — μU/ml‡	15±13	15±21	0.84
Intravenous glucose therapy — no. (%)	28 (14)	22 (11)	0.36
Hypoglycemia — no. (%)	18 (9)	12 (6)	0.25
Hypocalcemia — no. (%)	2 (1)	2 (1)	0.99
Hyperbilirubinemia — no. (%)	12 (6)	8 (4)	0.36
Polycythemia — no. (%)	4 (2)	6 (3)	0.52
Lung complications — no. (%)	16 (8)	12 (6)	0.43
Respiratory support — no. (%)	4 (2)	6 (3)	0.52
Admission to neonatal intensive care unit — no. (%)	12 (6)	14 (7)	0.68
Congenital anomaly	5 (2)	4 (2)	0.74
<b>Perinatal mortality — no. (%)§</b>			
Stillbirth	1 (0.5)	1 (0.5)	0.99
Neonatal death	1 (0.5)	1 (0.5)	0.99

\*Plus-minus values are means ±SD.

†The ponderal index was calculated as 100 times the weight in grams divided by the cube of the length in centimeters.

‡To convert values for insulin to picomoles per liter, multiply by 6.0.

§Numbers include infants with congenital anomalies.

any infant, a result that confirms in vitro studies in which no maternofetal or fetomaternal transfer of glyburide was detected in full-term placentas perfused immediately after delivery.<sup>29-31</sup> In addition, glyburide has no effect on the placental transport and uptake of glucose, and maternal hyperglycemia does not alter the placental transfer of glyburide in vitro. The finding of similar cord-serum insulin concentrations in our two treatment groups also indicates that little if any glyburide reached the fetuses. In a single study of pregnant rats, the transfer of tritium-labeled glyburide across the placenta was detected.<sup>49</sup> However, these findings may be due to differences in placental permeability among species.

The use of oral sulfonylurea drugs in pregnant women has been limited, and therefore there is scant information on their efficacy.<sup>2-4</sup> The available data are from retrospective studies of small numbers of women, many of whom had diabetes before pregnancy.<sup>12-18,21,25</sup> In most of these studies, the frequency of perinatal death or congenital abnormalities was increased, and the proportion of infants who were large for gestational age was increased in three studies.<sup>16,21</sup> There are no reports of therapy with thiazolidinediones in pregnant women. Only one study of 33 women with type 2 diabetes reported the use of metformin. In this

small group, 18 percent of the infants were large for gestational age, 30 percent had jaundice, and 9 percent had major congenital anomalies.<sup>25</sup> In a randomized study of 151 women with gestational diabetes, 58 received chlorpropamide, 46 tolbutamide, and 47 insulin. The sulfonylurea drugs were not associated with higher perinatal mortality or congenital abnormalities than was insulin.<sup>20</sup> The women in our study were treated with glyburide well after organogenesis, and the rates of anomalies were similar in both groups and similar to previously reported rates of congenital anomalies in infants born to women without gestational diabetes.<sup>1</sup> We conclude that glyburide is an effective alternative to insulin in women with gestational diabetes.

## REFERENCES

- Langer O, Rodriguez DA, Xenakis EMJ, McFarland MB, Berkus MD, Arrendondo F. Intensified versus conventional management of gestational diabetes. *Am J Obstet Gynecol* 1994;170:1036-47.
- Diabetes and pregnancy. ACOG technical bulletin. No. 200 (replaces no. 92). Washington, D.C.: American College of Obstetricians and Gynecologists, December 1994:359-66.
- American Diabetes Association. Gestational diabetes mellitus. *Diabetes Care* 1998;21:Suppl 1:S60-S61.
- Metzger BE, Coustan DR, Organizing Committee. Summary and recommendations of the Fourth International Workshop-Conference on Gestational Diabetes. *Diabetes Care* 1998;21:Suppl 2:B161-B167.
- Kemball ML, McIver C, Milner RDG, Nourse CH, Schiff D, Tiernan JR. Neonatal hypoglycaemia in infants of diabetic mothers given sulphonylurea drugs in pregnancy. *Arch Dis Child* 1970;45:696-701.
- Lebovitz HE. Insulin secretagogues: old and new. *Diabetes Rev* 1999;7(3):139-53.
- Farquhar JW, Isles TE. Hypoglycemia in newborn infants of normal and diabetic mothers. *S Afr Med J* 1968;42:237-45.
- Zucker P, Simon G. Prolonged symptomatic neonatal hypoglycemia associated with maternal chlorpropamide therapy. *Pediatrics* 1968;42:824-5.
- Smok IW. Teratogenic effects of chlorpropamide in mouse embryos *in vitro*. *Teratology* 1992;45:474. abstract.
- Denno KM, Sadler TW. Effects of the biguanide class of oral hypoglycemic agents on mouse embryogenesis. *Teratology* 1994;49:260-6.
- Smok IW, Sadler TW. Embryopathic effects of short-term exposure to hypoglycemia in mouse embryos *in vitro*. *Am J Obstet Gynecol* 1990;163:619-24.
- Douglas CP, Richards R. Use of chlorpropamide in the treatment of diabetes in pregnancy. *Diabetes* 1967;16:60-1.
- Jackson WPU, Campbell GD, Notelovitz M, Blumsohn D. Tolbutamide and chlorpropamide during pregnancy in human diabetics. *Diabetes* 1962;11:Suppl:98-101.
- Sutherland HW, Bewsher PD, Cormack JD, et al. Effect of moderate dosage of chlorpropamide in pregnancy on fetal outcome. *Arch Dis Child* 1974;49:283-91.
- Coetzee EJ, Jackson WPU. Oral hypoglycaemics in the first trimester and fetal outcome. *S Afr Med J* 1984;65:635-7.
- Idem*. Pregnancy in established non-insulin-dependent diabetics: a five-and-a-half year study at Groote Schuur Hospital. *S Afr Med J* 1980;15:795-802.
- Notelovitz M. Oral hypoglycaemic therapy in diabetic pregnancies. *Lancet* 1974;2:902-3.
- Dolger H, Bookman JJ, Nechemias C. The diagnostic and therapeutic value of tolbutamide in pregnant diabetics. *Diabetes* 1962;11:Suppl:97-8.
- Malins JM, Cooke AM, Pyke DA, Fitzgerald MG. Sulfonylurea drugs in pregnancy. *BMJ* 1964;2:187.
- Notelovitz M. Sulphonylurea therapy in the treatment of the pregnant diabetic. *S Afr Med J* 1971;45:226-9.
- Sutherland HW, Stowers JM, Cormack JD, Bewsher PD. Evaluation of chlorpropamide in chemical diabetes diagnosed during pregnancy. *BMJ* 1973;3:9-13.
- Chlorpropamide in diabetic pregnancy. *Lancet* 1974;2:32.
- Jackson WPU, Campbell GD. Chlorpropamide and perinatal mortality. *BMJ* 1963;2:1652.
- Coetzee EJ, Jackson WPU. The management of non-insulin-dependent diabetes during pregnancy. *Diabetes Res Clin Pract* 1986;1:281-7.
- Idem*. Metformin in management of pregnant insulin-dependent diabetics. *Diabetologia* 1979;16:241-5.
- Piacquadro K, Hollingsworth DR, Murphy H. Effects of in-utero exposure to oral hypoglycaemic drugs. *Lancet* 1991;338:866-9.
- Steel JM, Johnstone FD. Sulphonylureas in pregnancy. *Lancet* 1991;338:1222.
- Gerich JE. Oral hypoglycemic agents. *N Engl J Med* 1989;321:1231-45. [Erratum, *N Engl J Med* 1990;322:71.]
- Elliott BD, Langer O, Schenker S, Johnson RF. Insignificant transfer of glyburide occurs across the human placenta. *Am J Obstet Gynecol* 1991;165:807-12.
- Elliott BD, Schenker S, Langer O, Johnson R, Prihoda T. Comparative placental transport of oral hypoglycemic agents in humans: a model of human placental drug transfer. *Am J Obstet Gynecol* 1994;171:653-60.
- Elliott BD, Langer O, Schuessling F. Human placental glucose uptake and transport are not altered by the oral antihyperglycemic agent metformin. *Am J Obstet Gynecol* 1997;176:527-30.
- Carpenter MW, Coustan DR. Criteria for screening tests for gestational diabetes. *Am J Obstet Gynecol* 1982;144:768-73.
- Langer O, Anyaegbunam A, Brustman L, Guidetti D, Mazze R. Gestational diabetes: insulin requirements in pregnancy. *Am J Obstet Gynecol* 1987;157:669-75.
- Langer O, Berkus M, Brustman L, Anyaegbunam A, Mazze R. Rationale for insulin management in gestational diabetes mellitus. *Diabetes* 1991;40:Suppl 2:186-90.
- Langer O. Maternal glycemic criteria for insulin therapy in gestational diabetes mellitus. *Diabetes Care* 1998;21:Suppl 2:B91-B98.
- Langer O, Mazze RS. Diabetes in pregnancy: evaluating self-monitoring performance and glycemic control with memory-based reflectance meters. *Am J Obstet Gynecol* 1986;155:635-7.
- Langer O, Levy J, Brustman L, Anyaegbunam A, Merkatz R, Divon MY. Glycemic control in gestational diabetes mellitus — how tight is tight enough: small for gestational age versus large for gestational age? *Am J Obstet Gynecol* 1989;161:646-53.
- Berkus M, Conway D, Langer O. The large fetus. *Clin Obstet Gynecol* 1999;42:766-84.
- Corbet A, Bucciarelli R, Goldman S, Mammel M, Wold D, Long W. Decreased mortality rate among small premature infants treated at birth with a single dose of synthetic surfactant: a multicenter controlled trial. *J Pediatr* 1991;118:277-84.
- Kang IS, Siler-Khodr TM. Effect of exogenous arachidonic acid and enzyme inhibitors on placental prostanoid production. *Placenta* 1993;14:341-53.
- Rydberg TY, Wahlin-Boll E, Melander A. Determination of glibenclamide and its two major metabolites in human serum and urine by column liquid chromatography. *J Chromatogr* 1991;564:223-33.
- Emilsson H, Sjoberg S, Svedner M, Christenson I. High-performance liquid chromatographic determination of glibenclamide in human plasma and urine. *J Chromatogr* 1986;383:93-102.
- Rouse DJ, Owen J, Goldenberg RL, Cliver SP. The effectiveness and costs of elective cesarean delivery for fetal macrosomia diagnosed by ultrasound. *JAMA* 1996;276:1480-6.
- Groop L, Luzi L, Melanger A, et al. Different effects of glyburide and glipizide on insulin secretion and hepatic glucose production in normal and NIDDM subjects. *Diabetes* 1987;36:1320-8.
- Groop L, Barzilai N, Ratheiser K, et al. Dose-dependent effects of glyburide on insulin secretion and glucose uptake in humans. *Diabetes Care* 1991;14:724-7.
- DeFronzo RA, Simonson DC. Oral sulfonylurea agents suppress hepatic glucose production in non-insulin-dependent diabetic individuals. *Diabetes Care* 1984;7:Suppl 1:72-80.
- Rossetti L, Giaccari A, DeFronzo RA. Glucose toxicity. *Diabetes Care* 1990;13:610-30.
- Simonson DC, Ferrannini E, Bevilacqua S, et al. Mechanism of improvement in glucose metabolism after chronic glyburide therapy. *Diabetes* 1984;33:838-45.
- Sivan E, Feldman B, Dolitzki M, Nevo N, Dekel N, Karasik A. Glyburide crosses the placenta *in vivo* in pregnant rats. *Diabetologia* 1995;38:753-6.