Relationship of Maternal and Fetal Outcome to Glucose Tolerance During Pregnancy in Whites and Indian Asians

Naylor's (1) timely review on diagnosing gestational diabetes emphasizes the need to reevaluate established criteria and find better diagnostic tests and criteria for the future. Several variables may confound the interpretation of an oral glucose tolerance test (OGTT) during pregnancy, and ethnicity is one such factor (2), especially if the ethnic group in question has an overall high prevalence of diabetes. Great Britain has a large immigrant population from the Indian subcontinent. Indian Asians have a significantly higher prevalence of diabetes compared with the indigenous White population (3).

We studied 554 consecutive pregnancies (356 Whites, 198 Indian Asians) who had a 75-g OGTT in the third trimester of pregnancy from the 28th to the 32nd wk. These were analyzed for maternal (toxemia of pregnancy, cesarean sections) and fetal (macrosomia, microsomia, congenital abnormalities, perinatal mortality, prematurity) complications according to a 2-h venous plasma glucose stratified as follows: 4.0, 4.1–5.0, 5.1–5.5, 5.6–6.6, 6.7–7.7, 7.8–11.0, and 11.1 mM. Our results were previously published in detail (4) and are summarized as follows. In Whites, fetal complications ranged from 19 to 40%, and maternal complications ranged from 7 to 40%, but there was no relationship to 2-h blood glucose in either case. In Indians, fetal complications in each stratified group were 33, 10, 23, 12, 4, 50, and 10% and maternal complications were 0, 17, 19, 21, 1, 45, and 20%.

There was a significant linear trend in proportions of Indian Asian maternal complications as glucose concentrations increased ($P < 0.05$; 5). There was also a significant overall difference in Indian Asian fetal complications ($P < 0.01$), with a higher prevalence at the ends of the glycemic range. The World Health Organization suggested that the same criteria should be applied for interpreting an OGTT during pregnancy as in the nonpregnant state (6). There is some evidence that even within the so-called normal range, increasing degrees of glycemia may confer an added risk to pregnancy (7). Our study emphasized that, not only do new criteria for gestational diabetes need to be derived, but also these need to be validated especially in differing ethnic groups before they are universally recommended. In Whites, fetal and maternal complications were common if 2-h plasma glucose levels were >11.1 mM (40% for either complication), but for Indians, the major risk appeared to be at ≥7.8 mM (38% for either complication).

One hundred seventy Whites with 2-h plasma glucose levels ranging from <4.0 to 5.5 mM had 38 (22%) pregnancies with fetal complications and 18 (11%) pregnancies with maternal complications. This was compared with the Indian Asian population, which produced 15 (17%) pregnancies with fetal complications and 13 (15%) pregnancies with maternal complications. In the range 5.6–7.7 mM, 154 Whites produced 35 (23%) pregnancies with fetal complications and 19 (12%) pregnancies with maternal complications. In 80 Indian Asians, 7 (9%) pregnancies had fetal complications, and 14 (17%) pregnancies had maternal complications. Higher percentages were found in the range 7.8–11 mM; of 27 Whites, there were 6 (27%) complications in both groups compared to the Indian Asian total of 22 pregnancies, in which there were 11 (50%) fetal complications and 10 (45%) maternal complications. In those with 2-h plasma glucose levels >11.1 mM, of 5 Whites examined, 2 (40%) pregnancies had fetal and maternal complications, whereas of 10 Asians, 1 (10%) pregnancy had fetal complications and 2 (20%) pregnancies had maternal complications.

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Hemolytic Anemia Associated With Sulfonylurea Use

Case Study and Review of Literature

Herein, we report a case of glyburide-induced hemolytic anemia. The patient is a 53-yr-old female with a 3-yr history of non-insulin-dependent diabetes mellitus who has been on glyburide for >2 yr and presented with nonspecific complaints of nausea, weakness, and lethargy of 1 mo duration associated with hyperglycemic symptoms. Her self-monitored blood glucose (SMBG)

records showed many values of >11.2 mM. Her glyburide dose was increased from 10 to 15 mg/day. An HbA_{1c} obtained subsequently was only 4.0%. The discrepancy with the SMBG records raised the possibility of anemia. Glyburide was discontinued because of additional concerns that an adverse drug effect (either constitutional symptoms or hepatitis) could have accounted for her symptoms, and human insulin was started. Other laboratory results showed Hb 72 g/L, hematocrit 0.199, total bilirubin 44.5 μM, and lactic dehydrogenase 10 μkat/L. Her physical examination was normal. Hemolytic anemia was confirmed by a reticulocyte count of 15.8%, erythrocyte distribution width of 24.7%, haptoglobin <0.05 g/L, and a peripheral smear with marked anisocytosis, polychromasia, spherocytosis, Howell-Jolly bodies, and nucleated erythrocytes. Secondary causes of hemolytic anemia were ruled out with a rheumatoid factor of 5 IU/ml and CH_{50} of 53 U; complement and quantitative immunoglobulin levels were normal, and glucose-6-phosphate dehydrogenase screen was negative. Serological testing included a direct antiglobulin test (DAT), which was strongly positive with IgG but negative with C3b, C3d, and C4. The antibody was a single IgG with strong anti-e activity, found both in the serum and adhering to the patient's erythrocytes. The patient's serum did not agglutinate compatible erythrocytes that had been exposed to glyburide.

Prednisone was given to rapidly reverse the hemolysis. Her blood counts improved, and a prednisone taper was initiated. Follow-up at 1 and 3 mo showed continued improvement in the Hb, hematocrit, lactic dehydrogenase, and reticulocyte count, whereas the DAT became less strongly positive for IgG. At the 7 mo follow-up, the patient was off prednisone, and all biochemical and hematological measures had normalized.

Review of the previously reported cases of sulfonylurea-related immune hemolytic anemia have cited various mechanisms as causing hemolysis. Kopicky and Packman (1) reviewed five chlorpropamide-related cases. Each case was the result of immune complex–mediated hemolysis. In each, an IgG antibody directed against chlorpropamide was identified in low titers, and DAT showed no antibody on the erythrocytes. A positive antiglobulin reaction or cell lysis required the combination of the drug, patient serum, and fresh complement. Clinically, all cases presented acutely within 2 wk of therapy with a dramatic presentation of symptoms.

Two tolbutamide-related cases demonstrated evidence of hapten-mediated hemolysis (2,3). An IgG antibody directed against the drug was identified. Direct agglutination and antiglobulin reactions were positive only on drug-coated cells; addition of the drug to patient's serum neutralized the antibody's activity. Clinically, patients had a prolonged drug exposure (9–14 mo) before developing subacute symptoms and moderately severe hemolysis. There was in vitro cross-reactivity with other sulfonylureas for both the hapten and immune complex–mediated mechanisms of hemolysis.

One case of glyburide-induced hemolysis has been reported in which the authors suggested a cephalothin-type mechanism of nonimmunological protein absorption (4). The initial DAT was strongly positive for IgG and weakly positive for C3 and C4. After 6 mo, the DAT remained strongly positive for IgG but was negative for C3 and C4. These results are inconsistent with the suggested mechanism because at 6 mo there should not have been a strongly positive reaction with IgG. The most likely mechanism for our patient's hemolysis is an α-methyldopa type of drug-induced autoimmune hemolytic anemia based on *1*) a single IgG antibody with anti-e activity, both in serum and erythrocytes (which was in high titer initially and decreased subsequently), *2*) DAT strongly positive for IgG but not for C3 and C4, and *3*) the prolonged drug exposure before hemolysis. Characteristics of the antibody could also be consistent with idiopathic autoimmune hemolytic anemia. It is impossible to establish a methyldopa-type mechanism without rechallenging the patient with glyburide. However, ~10% of patients with aldomet-induced hemolytic anemia had serological tests that were indistinguishable from idiopathic hemolytic anemia (5). Also, the methyldopa-type mechanism could explain the persistently positive DAT for IgG in the previous glyburide-related case. Weak anticomplement activity may be seen in cases of aldomet-induced hemolytic anemia, and this could account for the initial anticomplement reaction described in the earlier glyburide-related case (6).

Although glyburide-induced hemolytic anemia may be quite rare, it is possible that mild hemolysis may be undetected in the routine care of diabetic patients. Low HbA_{1c} levels with correspondingly higher finger-stick values obtained at home should suggest hemolysis as a mechanism in patients treated with sulfonylureas.

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