

John B. O'Sullivan: A Pioneer in the Study of Gestational Diabetes

The increased obstetrical risk associated with diabetes first recognized in pregnancy, i.e., gestational diabetes, was first described in the postwar period by Dr. J. P. Hoet in a paper written in French and translated into English by Dr. F.D.W. Lukens for publication in *Diabetes* in 1954 (1). Not long after that the National Institutes of Health developed a program in the epidemiology of chronic disease, and a field center was established in Boston, Massachusetts, under Hugh Wilkerson (2). Dr. John B. O'Sullivan, having grown up in Ireland and graduated from the Royal College of Physicians and Surgeons in 1951, found his way to America and joined this program in the mid-late 1950s.

At the time there was a great controversy about how to diagnose gestational diabetes. Using oral glucose tolerance test (OGTT) criteria for nonpregnant subjects, the incidence of diabetes was as much as one-third of the entire pregnancy population. To address this question, O'Sullivan performed 100-g OGTTs in 752 mainly second- and third-trimester pregnant women and published the first, second, and third standard deviation upper limits for these glucose values (3). These were the first statistically based criteria for assessing the upper limit of glycemic normality in pregnancy. These criteria differed from those in normal individuals by having higher upper-limit values at the 2nd and 3rd hours, consistent with an impaired glucose tolerance in pregnant compared with nonpregnant individuals. This result was consistent with the earlier observation of higher glucose values after oral glucose administration in pregnant women published by Hurwitz and Jensen in the *New England Journal of Medicine* in 1946 (4). The O'Sullivan criteria, published with statistician Claire Mahan, were the standard for diabetes detection in pregnancy for the next 40 years (3).

In the ensuing years, O'Sullivan and Mahan used the criteria to detect gestational diabetes and then to determine

whether insulin therapy could ameliorate the condition. In this work, they found that insulin could reduce infant macrosomia incidence, a leading indicator of the diabetic diathesis in pregnancy (5). The follow-up studies conducted by O'Sullivan's group at the Boston City Hospital in the 1960s allowed for very-long-term follow-up of the early pregnancy cohort, showing that ~50% of the women diagnosed with gestational diabetes would become intolerant to glucose by nonpregnancy-defined criteria in subsequent years, reaching an asymptote at ~10 years postpartum (5–7).

Interest in the pathophysiology and significance of gestational diabetes grew gradually in the 1970s. The physiological studies of Freinkel and associates were begun at the Harvard Medical Unit of Boston City Hospital and then at Northwestern University (8). The work of O'Sullivan and others was reviewed under the auspices of the Food and Nutrition Board of the National Academy of Science in the late 1970s (9). Shortly after, the O'Sullivan criteria were endorsed by the National Diabetes Data Group (NDDG), and widespread screening for gestational diabetes using these criteria became established across the country by the mid-1980s (10). As more studies have been performed, morbidity surrounding gestational diabetes has become a more significant end point than mortality and has extended beyond simple macrosomia (11,12). Using this approach (12), evidence has been obtained for the identification of at-risk pregnancies using the more inclusive criteria defined by Carpenter and Coustan (13).

Presently the field of gestational diabetes remains in great need of clinical trials evaluating specific approaches to therapy, comparing, for instance, exercise and nutrition therapy; nutrition therapy, oral agents, and insulin; or combinations thereof (14–18). Larger numbers of subjects need to be studied for a more discreet appreciation of the incidence of low-frequency morbidities. An international

observational study, Hyperglycemia and Adverse Pregnancy Outcome, will attempt to confirm the presence of perinatal morbidities in gestational diabetes versus healthy pregnancy across national boundaries. However, the intellectual clarity and mathematical and epidemiological discipline shown in the path-breaking work of O'Sullivan and Mahan still serves as a guide for investigators who work in the field.

Those of us fortunate enough to have participated in the Western Diabetes and Pregnancy Study Group meeting in Seattle in 1993 heard Dr. O'Sullivan's review of his work. His good humor, common sense, and intellectual discipline were seen at this meeting, interrupted by visits to Kells, the local Pike Place Market Irish pub, for an Irish song or two.

Dr. O'Sullivan died at home in Wellesley, MA, in August 2001, attended by his wife, Ann, his four children, and his five grandchildren. He was 75 years of age. Although he had other careers as the director of employee health nationwide at Liberty Mutual Insurance Company; as advisor to the National Institutes of Health diabetes and disease prevention programs, including the Lipid Research Clinics Program; and as a clinician at the Boston City Hospital Diabetes Clinic, and also published in the area of arthritis epidemiology, Dr. O'Sullivan's greatest love was the research of early diabetes as manifested in pregnancy and in the nonpregnant state and its subsequent effects on health. The criteria of O'Sullivan and Mahan brought to American epidemiology sound observational and statistical science to establish definitions that have stood the test of time. The O'Sullivan criteria serve as a point of departure for all subsequent research in the field. Those of us who worked with Dr. O'Sullivan will always remember the man and his pioneering, independent, and uncompromising science.

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