

Chapter 2

The Framework

In the history of medicine major advances promising new-found health paradoxically have sometimes led to emergence of new disease. A significant instance of this advance and retreat is seen in the annals of diabetes mellitus, a record of human success in whose train there emerged tough new questions. Questions presented by our subjects, the embryos and newborn infants of pregnant diabetic women. The focus here is on the hazards faced by them, introduced by a main concern, death of the newborn.

Early Childhood Death

One of the much trumpeted social and medical achievements of the twentieth century is the great reduction in the rate of deaths of children under the age of 1 year—by which the standard of civilization is customarily judged. Years ago it was declared that “a low rate...indicates a healthy community, a high rate the reverse” (Newman 1906) and “infant mortality is the most sensitive index we possess of social welfare...” (Newsholme 1910), a criterion that still reigns (Shapiro et al. 1965; Yankauer 1990).

Extraordinary progress thus shines forth from the precipitous decline in the mortality rate of children under 1 year of age, e.g. in the US, which went from 99.9 to 7.0 per 1000 children born alive—greater than 90%—in the 80 years or so following the end of the First World War (U.S. Bureau of the Census 1960; National Center for Health Statistics 1998). And the same great achievement was realized in many countries in Europe and elsewhere (Chase 1967; Thomson and Barron 1983). [It must be noted with curiosity that the US ranking in this statistic vis-à-vis the nations of the world is hardly better in 2010 than it was 100 years ago, in 1911, as noted at that time by S.W. Newmayer (Brosco 1999).]

The first month, but especially the first week, is the most perilous time of life, since that is when the most weak and damaged babies die. It is death in these first 7 postnatal days, plus that in the last weeks of pregnancy—together known as the perinatal period—that is of great relevance here. These earliest deaths also greatly

participated in the great decline, falling in the US from 32.5 per 1000 live births and fetal deaths in 1950 to 6.6 in 2005 (Powell-Griner 1986; MacDorman and Kirmeyer 2009).

This reduction was largely brought about by the virtual elimination of many public health problems and pediatric diseases. But advance was most uneven. At the same time that many widespread causes of neonatal and infant death, disability, and distress—hygienic, nutritional, infectious—were so impressively ameliorated barely any headway was made with others.

The Role of Diabetes

The momentous discovery of insulin in 1921 (Banting and Best 1923) and its wide availability afterward (Wrenshall et al. 1962; Bliss 1982) soon had profound effects, loosing a cascade of consequences. First the barrier to reproduction by women with this disease was greatly lowered. But then, as the number of pregnancies of diabetic women increased, it was seen that many of their infants did not survive long. Which abated as some of the reasons for the perinatal deaths were discovered and successfully managed.

But with this ongoing decline a shift occurred in the cause of the deaths that continued to occur, this residue in fact growing in importance. What soon became, and has continued to be, among the chief causes of this offspring death were congenital malformations. And as these proved to be largely unpreventable they received increasing attention—especially as suspicion arose that maternal diabetes itself may be their cause.

Diabetes mellitus when present in early pregnancy profoundly affects the viability, growth, and development of the unborn. This work will trace the ideas and practices that have evolved over the years in the attempt to manage these difficulties. It will consider some of the most perplexing of the imperfectly answered or still unanswered of these problems, most prominent among them: whether diabetes causes or is associated with spontaneous abortion, retarded prenatal growth, and congenital malformations, whether such malformations form distinctive patterns, the relation between malformation and perinatal death, whether the form and degree of the maternal disease or its presymptomatic stages are related to these phenomena, and whether control of the disease from before or early in pregnancy can lessen these hazards.

For reasons to be seen the decade of the 1950s can be taken as a watershed in the ongoing progress in the treatment and outcome of diabetic pregnancy. Thus the events and problems encountered in dealing with these pregnancies before insulin was discovered and those emerging in the years between this discovery and the 1950s will introduce the subject.

[Methodological and conceptual matters must be noted. The definition of congenital malformations followed by diabetologists, obstetricians, and pediatricians has not always been clear or uniform; ascertainment of pregnant diabetic women

(i.e. avenues of their selection for study and treatment) was often biased; no controls or poorly matched controls were usually the case (Rubin and Murphy 1958; Wilson 1960; Simpson 1978; Mills 1982). Such considerations make it necessary first to deal with definition and classification of congenital malformations, diabetes in pregnancy, etc.]

Data Sources

The main source of information used here were reports of pregnancies of diabetic women by hospital-based physicians in the US, Canada, and many European countries. They were identified by searching the medical literature, using the Quarterly Cumulative Index Medicus for older ones, Internet sources, and, most usefully—however biased they may have been—the citations in the reports themselves, providing the trail to older and older publications. Consulted also were reports of multicenter, population, and epidemiological surveys, and public-health matters with respect to the births of diabetic women.

The advantages of hospital-based reports compared with vital-statistics and other such data are that they are more complete (judging from the underreporting public records commonly suffer from; see e.g. Greb et al. 1987; Snell et al. 1992); usually providing information otherwise lacking, such as detailed descriptions of individual pregnancies and offspring, and are more informative, especially sometimes being supported by autopsy records.

Hospital-based studies however also had their drawbacks, requiring cautious interpretation of their findings. An important problem was that the composition of the patients served by different hospitals varied, demographically, medically, and so on, some of which were without doubt relevant here. For example, some hospitals were primary-care facilities, whose patients were drawn from their immediate communities and for the most part were representative of the disease picture of its population. Other reports were from larger hospitals or specialized medical facilities many of whose patients were referred from hospitals in the area or from outside the area altogether. These patients were no doubt less representative of the spectrum of the illness present in the entire population. How must the facts from such different sources be handled? The problems of procedure and interpretation that these and other uncertainties presented will be considered below.

Definition

A full definition of diabetes in pregnancy will be detailed below. Here only a few general remarks are necessary. Diabetes mellitus is the omnibus term given to what are probably several etiologically distinct disorders of carbohydrate metabolism, characterized by chronic hyperglycemia, in which there is usually an absolute or

relative deficiency of insulin or its reduced secretion or impaired action. The disease predominantly occurs in two generally distinct forms, denoted type 1, insulin dependent, mostly of juvenile onset, and type 2, noninsulin dependent, mostly of maturity or adult onset, further discussed below (National Diabetes Data Group 1979; World Health Organization 1985).

In addition to the general classification another exists for diabetes in pregnancy. This also has two broad categories: diabetes that antedates pregnancy, often called pregestational diabetes, and diabetes that first occurs during pregnancy, called gestational diabetes. These also will be elaborated upon below. Both forms may be either insulin dependent or independent, but the former is most often dependent and the latter most often independent. [Exceptions—there are always exception—to general pronouncements, which will emerge as the writing progresses.]

The untoward outcomes of diabetic pregnancy that are the main concern here—spontaneous abortion, fetal and neonatal death, and congenital malformation—are associated almost entirely with insulin dependent pregestational diabetes. For the sake mostly of developing the historical picture of the subject gestational diabetes and related topics will also be considered. But the main focus will be on the pregestational insulin dependent variety, and hence when the unqualified term ‘diabetes’ is used it will refer to that variety.

A History of Diabetes in Pregnancy

The impact of maternal diabetes on offspring prenatal
development and survival

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