THE HEFTY FETAL TYPE HYPOTHESIS

THE ROLE OF DIABETIC PREGNANCIES AND EXCESS INTRAUTERINE NUTRITION IN THE EPIDEMIC OF TYPE 2 DIABETES AMONG INDIGENOUS PEOPLES

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North America aboriginal people, and other indigenous peoples worldwide, are experiencing an epidemic of type 2 diabetes mellitus (T2DM) and its complications. Both genetic and environmental factors have been implicated in this epidemic, but the possible diabetogenic role of the intrauterine milieu has also attracted increasing attention. Most attention has focused on the relationship between low birth weight (LBW) and T2DM [1,2]. For example, the widely quoted thrifty phenotype hypothesis suggests that impaired islet cell development caused by maternal/fetal malnutrition increases the risk for T2DM in adulthood.

While conditions leading to fetal malnutrition and LBW may be important for the subsequent development of T2DM under certain circumstances and in some populations, they are unlikely to explain the rapidly increasing rates of T2DM in populations experiencing acculturation. We believe that recent findings from our work, and evidence from research among the Pima Indians, now suggest that excess, rather than inadequate, fetal nutrition may have become the overriding intrauterine factor in the pathogenesis of T2DM among Canadian, and possibly other, indigenous peoples. A key element in this hypothesis is the role of diabetes (gestational diabetes and T2DM), as well as gestational-impaired glucose intolerance (GIGT), during pregnancy.

We first became intrigued by the possible role of gestational diabetes (GDM) in the epidemic of T2DM among Saskatchewan aboriginal people in the early 1990s, when we conducted a diabetes prevalence study on three northern Saskatchewan reserves [3]. Although we found that rates of T2DM paralleled increasing rates of obesity, the overall prevalence of T2DM was still quite low. In contrast, an unexpected finding was that rates of GDM, up to 15%, were several times higher than those reported in the general population, about 3%. While others had also observed high rates of GDM in aboriginal populations, this was the first time that it had been noted in communities in which T2DM was uncommon. We therefore speculated that GDM might be one of the earliest manifestations of carbohydrate intolerance in some aboriginal populations as they experience acculturation and a dramatic change in lifestyle. We also wondered whether the high rates of GDM that we had observed could be an important contributing factor in the initiation and progression of the T2DM epidemic in these populations. This has led to a decade-long search for answers to these questions.

High birth weigh (HBW) is a frequent complication of GDM and of pregnancy in women with preexisting diabetes. We therefore reasoned that if the appearance of GDM were one of the earliest stages in the T2DM epidemic among Saskatchewan aboriginal people, we ought to find that increasing rates of HBW had preceded overt T2DM in this population. Subsequently, we were excited to find that HBW rates had increased from 12.6% to 19.2% between 1975 and 1984 in northern Saskatchewan (predominantly aboriginal), but from only 10.2% to 12.8% in the south (predominantly non-aboriginal) [4]. This was consistent with a Canadian Inuit/Indian survey that had reported an increase in HBW rates from 12 to 22 % over the period of 1962 to 1983.

We were aware of the seminal work done in the southwestern United States showing that the offspring of Pima women with T2DM and GDM had increased rates of HBW and a propensity to develop early age

onset T2DM [6]. Our next step, therefore, was to conduct a case-control study, in which we examined the relationship between HBW (>4000 g) and the future development of T2DM among adult registered Indian in Saskatchewan. Our recent report showed for the first time that Canadian aboriginal people with diabetes are significantly more likely than control populations to have been born with HBW [7]. The association between HBW and T2DM strengthened progressively from the middle to late 20th century, suggesting that HBW and its causes may be assuming an ever more important role in the T2DM epidemic. It may also suggest that the younger the age of T2DM diagnosis in this population, the stronger its relationship with HBW.

What has slowly emerged during our investigations has been the development of a new paradigm that we have termed the hefty fetal phenotype (or "hefty fetal type") hypothesis [7]. This is a unifying concept that is consistent with the thrifty genotype hypothesis [8] and integrates an expanding and diverse body of information from our own and others' research. Neel first proposed that a thrifty genotype conferred a survival advantage on populations subject to periods of nutritional hardship by favoring caloric conservation when food was abundant. He suggested that this had now become a liability because, in modern times, it contributes to obesity and T2DM when combined with nutritional excess and decreased physical activity. We now speculate that the thrifty genotype would be particularly advantageous for a population's survival if it increased the likelihood of successful pregnancies. By favoring caloric conservation in women of childbearing age, as well as in their unborn children, the thrifty genotype would optimize fetal nutrition and promote a "healthy" birth weight. However, with the surfeit of food associated with modern times, it could predispose to T2DM and GDM in young women and the subsequent development of HBW in their children. To support this conjecture, we have most recently shown that aboriginal ethnicity is an independent risk factor for GDM in Saskatchewan aboriginal women when combined with pre-pregnancy obesity [9].

The pieces to this overall puzzle are slowly being put into place. An insulin-resistant state similar to T2DM appears to be characteristic of normal pregnancy but can result in GIGT or GDM if demands for increasing insulin production are excessive [10,11]. GDM-related hyperglycemia causes fetal hyperinsulinemia, accelerated fuel utilization and macrosomia [12]. The fetal metabolic and anthropometric changes that result from this could persist and contribute to the development of insulin resistance in adulthood [13]. Thus, what may have evolved as a survival advantage for newborns and their mothers has now become a metabolic liability for both. Accordingly, we speculate that the phenomenon that we have described plays a pivotal role in the early stages, as well as the perpetuation of, the T2DM epidemic in aboriginal peoples.

What are the implications of the "hefty fetal type" hypothesis? If confirmed, targeting modifiable risk factors for GDM/GIGT [14] and establishing programs to diagnose and optimally manage diabetes during pregnancy could constitute a breakthrough in halting the exponential transfer of risk for T2DM and its complications in successive generations of aboriginal peoples.

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