

# The global increase in diabetes: Unique issues for mothers and children

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It is now well documented that obesity and diabetes mellitus (DM) are increasing globally in epidemic proportions across all age groups. As a result, type 2 DM is for the first time being seen frequently in children and young adults in many populations. An increase in the incidence of gestational diabetes mellitus (GDM) has also been well documented in Australia and the United States, and there are some data suggesting the same trend in India. However, universal screening for GDM is not practiced in many areas of the world, making it difficult to estimate its true prevalence. The increase in type 2 DM in youth has implications beyond the burgeoning number of persons affected. First, the younger the patient at onset of disease, the greater is the lifetime risk of developing complications of diabetes and/or cardiovascular disease. Secondly, intrauterine exposure to the metabolic environment of maternal diabetes, or GDM, is associated with increased risk of obesity and altered glucose homeostasis (impaired fasting glucose, impaired glucose tolerance and type 2 DM) in the offspring, beginning in childhood and probably reflected in more GDM in the next generation as well. In addition, impaired intrauterine growth (under-nutrition) is associated with a similar childhood phenotype and similar adult chronic disease risks. Thus, alterations in the intrauterine metabolic environment may be important contributing factors to the ongoing epidemics of obesity and type 2 diabetes.

**KEY WORDS:** Diabetes in women, effects on children, gestational diabetes, intrauterine influences of diabetes.

## Introduction

Reports from many sources indicate that type 2 diabetes mellitus (T2DM) is increasing at a rapid rate throughout the developed and developing world. Hilary King and colleagues have carefully analyzed published reports and introduced adjustments for variation in age to develop the most comprehensive estimates currently available.<sup>[1]</sup> The 1995 estimated global burden of DM was 135.3 million persons. This was projected to reach >300 million in 30 years (2025). By virtue of a relatively high T2DM incidence and its large population, in 1995 India had the unenviable distinction of being the country with the greatest number of persons with diabetes and is projected to experience nearly a threefold increase in cases between 1995 and 2025. The 1995 estimates and projections for 2025 in 10 countries contributing the largest proportions of cases of DM are shown in Table 1.

The factors responsible for the rapid increase in the number of persons with type 2 DM are not fully known,

**Table 1: The worldwide epidemic of diabetes mellitus\***

| 1995 estimates | N = Million | 2025 projections | N = Million |
|----------------|-------------|------------------|-------------|
| India          | 19.4        | India            | 57.2        |
| China          | 16.0        | China            | 37.6        |
| United States  | 13.9        | United States    | 21.9        |
| Russian Fed.   | 8.9         | Pakistan         | 14.5        |
| Japan          | 6.3         | Indonesia        | 12.4        |
| Brazil         | 4.9         | Russian Fed.     | 12.2        |
| Indonesia      | 4.5         | Mexico           | 11.7        |
| Pakistan       | 4.3         | Brazil           | 11.6        |
| Mexico         | 3.8         | Egypt            | 8.8         |
| Ukraine        | 3.6         | Japan            | 8.5         |
| All others     | 49.7        | All others       | 103.6       |
| Total          | 135.3       | Total            | 300.0       |

\*King *et al.* Diabetes Care 21:1414-31, 1998<sup>[1]</sup>

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leading to much speculation. Strong familial aggregation of type 2 DM and high concordance for DM observed among identical twins indicate the importance of genetic factors. However, it is not plausible that rapid change in genetic susceptibility for type 2 DM accounts for the increasing prevalence of DM globally. An increase in average age of the population is an important and nonmodifiable factor that contributes to the overall increase in the total burden of type 2 DM; however, the incidence is increasing among all age groups, including adolescents, among whom type 2 DM was formerly very rare. Recent and emerging changes in lifestyle are most frequently implicated, though the magnitude of effect is difficult to estimate. Increase in frequency and severity of obesity and more sedentary lifestyle are strongly associated with higher risk of developing type 2 DM. Primary and confirmatory data are available from clinical and epidemiological sources in many parts of the world. For example, changes in obesity among youth in the USA have been well documented by Centers for Disease Control reports and illustrated in Table 2. In the 25 years between 1974 and 1999, overweight (BMI >95%) in children 6-9 years of age increased more than threefold and between 1980 and 1999, the same magnitude of increase occurred in 12-19 year olds.<sup>[2]</sup>

## Pregnancy and Diabetes

In the midst of the global increase in diabetes, it is expected that diabetic pregnancy would also be seen more frequently. With optimal DM control before and throughout gestation, perinatal outcome in diabetic pregnancy approaches that of the general obstetric population, except when DM is complicated by nephropathy, hypertension or cardiovascular disease.<sup>[3]</sup> In concert with these modern advances in obstetrical, medical and neonatal care, increasing numbers of women with type 1 DM have had successfully completing pregnancies for the last 2-3 decades. In the last decade, pregnancy in women with type 2 DM has become more common, even among populations in which this was previously rarely seen. It would also be expected that the

incidence of gestational diabetes mellitus (GDM), a common forerunner of type 2 DM in women, would also be documented. However, universal screening for GDM is not routinely practiced in many parts of the world, and diagnostic tests and criteria are not standardized. Evidence for an increase in GDM was reported from Australia more than a decade ago.<sup>[4]</sup> The data summarized in Table 3 were reported from the Kaiser Permanente Health Plan of Northern California in early 2004.<sup>[5]</sup> In this program, screening for GDM is standardized and applied universally with >85% compliance with the protocol. These data are derived from more than 265,000 pregnancies that were screened for glucose intolerance. During the 10-year period from which these data are reported, the overall incidence (using the Carpenter-Coustan criteria throughout) showed an increase of 41%, adjusting for the influences of maternal age and ethnic mix. Similar findings have very recently been reported from the years 1994-2002 in a multi-ethnic population enrolled in Kaiser Permanente of Colorado.<sup>[6]</sup> An increase in GDM has also been reported in India<sup>[7]</sup>; however, detailed data on population-wise incidence from prior and current years are lacking.

Nevertheless, from the several trends cited above, it is reasonable to conclude that more newborn infants each year are being exposed to the metabolic environment of diabetes during intrauterine development as a result of changing incidence and demographics of diabetes and pregnancy.

## Health of women after having GDM

Increased risk of diabetes outside of pregnancy among women that have had GDM has been documented among many populations and ethnic/racial groups. Indeed, the establishment of GDM as a diagnostic entity following the pioneering work of O'Sullivan and colleagues<sup>[8]</sup> was based on criteria that identified women at risk for diabetes in the future. In recent years, several reports have established that at least in urban US populations,<sup>[9,10]</sup> the

**Table 2: Prevalence of overweight among children and adolescents in the United States\***

| Age (Years) | 1963-70 (%) | 1971-74 (%) | 1976-80 (%) | 1988-94 (%) | 1999 (%) |
|-------------|-------------|-------------|-------------|-------------|----------|
| 6-11        | 4.2         | 4.0         | 6.5         | 11.3        | 15.3     |
| 12-19       | 4.6         | 6.1         | 5.0         | 10.5        | 15.5     |

\*From data provided by Center for Disease Control and Prevention, National Center for Health Statistics and National Health and Nutrition Examination Survey<sup>[2]</sup>

**Table 3: Increasing incidence of gestational diabetes in Northern California (1991-2000)\***

| Year                              | 1991 (%) | 1993 (%) | 1995 (%) | 1997 (%) | 2000 (%) |
|-----------------------------------|----------|----------|----------|----------|----------|
| All ethnic groups <sup>†</sup>    | 5.1      | 5.2      | 6.2      | 7.5      | 7.2      |
| White (Non-Hispanic) <sup>†</sup> | 3.9      | 4.1      | 5.1      | 5.7      | 5.7      |
| African American <sup>†</sup>     | 4.1      | 5.1      | 4.7      | 5.8      | 6.4      |
| Hispanic <sup>†</sup>             | 7.2      | 6.9      | 8.1      | 9.8      | 8.3      |
| Asian <sup>†</sup>                | 7.2      | 8.0      | 8.3      | 11.0     | 9.7      |

\*Adapted from: Ferrara A. *et al*: *Obstet Gynecol* 103:526-33, 2004<sup>[5]</sup>

<sup>†</sup>Adjusted for age and race-ethnicity, <sup>‡</sup>Adjusted for age

rate of progression to DM is very high within 5 years following the diagnosis of GDM. It is encouraging that the diabetes prevention program (DPP) and the Troglitazone Prevention of Diabetes studies<sup>[11,12]</sup> indicate that lifestyle intervention or medical therapy can prevent or delay the progression to DM after GDM.

Risk of cardiovascular disease (CVD) and associated morbidity and mortality among women with DM are known to be very high. Information about CVD in women that have had GDM is limited. The long-term follow-up study of O'Sullivan's original cohort of women with GDM did suggest that they were also at increased risk for development of CVD.<sup>[13]</sup> It is hoped that additional information on this important question will become available from the ongoing follow-up of the DPP cohort that included women with previous GDM.

### Children of mothers with diabetes or GDM

The 1980 Banting Lecture,<sup>[14]</sup> *Of Pregnancy and Progeny*, by the late Norbert Freinkel was a profound and provocative treatise. It pioneered the recognition that disturbances of the intrauterine metabolic environment potentially have major perinatal and/or long-term consequences. Furthermore, Freinkel stressed that both the type and time of the intrauterine insult have a major impact on the type and severity of resulting effect on the offspring. In the last 25 years, data from animal model studies, clinical observations and epidemiological reports<sup>[3]</sup> have validated the concepts that Freinkel had articulated so skillfully. Thus, it was established that metabolic control before and in the first 8 weeks after conception is a major determinant of the risks of fetal loss and major congenital malformations and that metabolic perturbations in the second and third trimesters of pregnancy influence neurological and psychological development of offspring of diabetic mothers.<sup>[15,16]</sup>

Freinkel was most intrigued by the hypothesis that intrauterine exposure to maternal diabetes has important lifelong implications on the development and function of adipose tissue and the regulation of glucose metabolism. Data from animal models<sup>[17]</sup> and early reports from epidemiological studies<sup>[18]</sup> are supportive of the concept. However, Norbert Freinkel's untimely death occurred before the conclusion of confirmatory clinical studies that he was instrumental in initiating.<sup>[15,16,19,20]</sup>

The National Institutes of Health (NIH) prospective, longitudinal study of diabetes among the Pima Indians

of Arizona was initiated 40 years ago. All members of the community are offered biannual oral glucose tolerance tests and anthropometric assessments from 5 years of age onward. This provides assessments of women before, during and after pregnancy and their offspring. Both obesity and type 2 DM are highly prevalent in the population. A comprehensive and outstanding series of papers provide conclusive evidence that intrauterine exposure to maternal diabetes (including GDM) predisposes the offspring to more severe, early onset obesity and substantially increases the risk of type 2 DM in children and young Pima adults.<sup>[21,22]</sup> Macrosomia or large for gestational age size is not required to convey these risks.<sup>[23]</sup> It has been estimated that 'exposure to the diabetic intrauterine environment was responsible for about 40% of type 2 diabetes in 5- to 19-year-old children between 1987 and 1996.'<sup>[24,25]</sup>

In the mid 1970s, an NIH-funded 'Diabetes in Pregnancy Center' (DPC) was established at Northwestern University in Chicago. The DPC performed metabolic, obstetric and neonatal observations on pregnant women with normal glucose metabolism or diabetes (preexisting and GDM) and initiated a prospective, longitudinal follow-up of the offspring. Anthropometric measurements were made at 6-month intervals, and from 2 years of age onward, an annual OGTT was offered. From 5-6 years of age onward, relative weight or BMI of offspring of mothers with both preexisting DM and GDM deviated progressively from the norm. Results of glucose tolerance tests were also informative. Few of the Chicago cohort (<2%) developed DM during the 18-20-year follow-up. Impaired glucose tolerance (IGT) was infrequent before age 5 years, began to increase during the 5-9 year window and was found in ~20% of those 10-16 years of age. By age 16, 40% of the ODM had IGT on one or more occasions. By contrast, IGT was found in <5% of nearly 100 adolescent controls.<sup>[20]</sup> Observations in the DPC cohort found fetal hyperinsulinism (identified by serial assessments of amniotic fluid insulin concentration) to be a strong, independent intrauterine marker of risk of both childhood obesity and IGT.<sup>[16,19,20]</sup>

The Chicago DPC cohort could not be followed beyond 18-20 years of age, and data are not systematically available from that cohort on pregnancies in the next generation. However, among the Pimas, the OGTT results during pregnancies of second generation differed in concert with glucose tolerance status during pregnancy of their mothers. When DM was present during

pregnancy in the first generation, more than two-thirds of offspring had abnormal glucose tolerance (DM or IGT) during their pregnancy.<sup>[26]</sup>

As suggested in Figure 1, the data summarized above indicate that by way of intrauterine exposure, '*Diabetes Begets Diabetes*.'<sup>[27]</sup> Since among the Pimas, 'exposure to the diabetic intrauterine environment was responsible for about 40% of type 2 diabetes in 5-19-year-old children between 1987 and 1996,'<sup>[24,25]</sup> Dr. Pettitt has referred to this as 'a vicious cycle.'<sup>[26]</sup> It is difficult to estimate the size effect of exposure to a diabetic intrauterine environment in other, more heterogeneous, populations that have lower and variable prevalence of obesity and glucose intolerance. However, the global increase in type 2 diabetes [Table 1] that extends across all age ranges [Tables 2 and 3] indicates that ever increasing numbers of individuals are being exposed to diabetes during intrauterine life.

### Other alterations of nutrition/growth and risk of obesity or diabetes

Historically, studies in which animal models were exposed to conditions of altered maternal nutrient composition and calories (in various combinations) before, during and after pregnancy provided strong evidence that these factors can influence growth and development during both intrauterine and later life of the offspring. Growth, development and propensities to obesity and diabetes have for many years been closely monitored in the individuals born to Dutch mothers

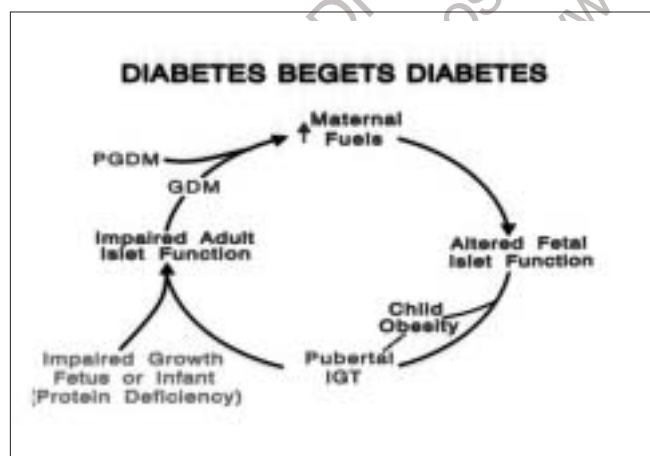


Figure 1: Illustrates the relationships between the altered intrauterine environment of diabetes (pregestational [PGDM] or gestational [GDM]) and the propensities to obesity and altered glucose metabolism beginning during childhood. It is also proposed that this will continue into adulthood, conveying risk for GDM. It is further suggested that the metabolic alterations associated with impaired growth during intrauterine life or infancy may also confer risk for GDM during reproductive years.

exposed to the wartime famine of 1944-45.<sup>[28]</sup> About 15 years ago, Hales and Barker first reported associations between small size (weight) at birth and/or 1 year of age and risk of CVD, obesity and glucose intolerance or diabetes among men in their sixth and seventh decades of life.<sup>[29,30]</sup> In subsequent years, similar associations have been found in numerous populations and locations around the globe. It is visualized that impaired intrauterine growth/nutrition results in the 'programming' of systems that regulate insulin sensitivity, insulin secretion and energy storage and utilization throughout the lifetime of the individual.

The factors most responsible for restricted fetal growth vary widely. In third world areas and among other impoverished populations, protein and/or calorie malnutrition are the predominant factors. In developed countries, growth restriction results from medical conditions that impair placental function and/or result in premature delivery. Although the causes and types of growth restriction are diverse, the associations with risks of adult obesity, CVD and diabetes seem to be similar. In the populations from which the birth weight-adult health associations were originally made, the small infants were predominantly 'term born.' In the last decade, resuscitation and survival of very low birth weight infants have increased substantially. Reports on development of such children are becoming available,<sup>[31]</sup> however, data on adult health of these individuals are lacking.

Numerous basic epidemiological and clinical efforts are ongoing in efforts to define the pathobiology and pathophysiology of fetal/newborn programming and to identify the 'risk factors' for the propensities for obesity, CVD and diabetes. Many important observations have been made by Dr. Yajnik and colleagues through their work in Pune, India. This group has found that leanness at birth (reduced, non-fat or lean-body mass) and fatness and/or tallness in childhood are strongly associated with insulin resistance.<sup>[32]</sup> The Avon Longitudinal Study of Pregnancy and Childhood study in the UK has reported that small lean infants that gain weight most rapidly or exhibit 'catch-up' growth are at the highest risk for obesity in late childhood.<sup>[33]</sup> Furthermore, an epidemiological study in Finland has found that the combination of small size at birth and obesity at age 11 represents high risk for CVD in adulthood.<sup>[34]</sup>

Formal studies of the rates of IGT/DM or GDM are not available in these cohorts. However, several reports suggest that those individuals that have impaired fetal



growth may contribute to the growing population at increased risk for GDM. In a study from South Korea, Jang and co-workers found that women with GDM tended to be shorter than their unselected population of pregnant women.<sup>[35]</sup> A similar association has been found in some, but not all, populations. Jang's study also found strong associations between year of birth, height of women and yearly incidence of GDM. The period of shortest stature coincided with the difficult period of the Korean War. Women born after 1960 and up to 1975 showed a nearly 3-cm increase in adult height. At the same time, the prevalence of GDM, adjusted for differences in maternal age, declined sharply. Data illustrating growth of gross national product (economic status) and the increase in height of the population can be superimposed. In the Pima cohort, data are available to examine the relationship between birth weight and risk of diabetes during pregnancy.<sup>[36]</sup> As predicted, the risk of diabetes during pregnancy was found to be several-fold higher in 15-24-year-old women whose own birth weight was >4 kg (a surrogate for maternal DM in this population) than among those whose birth weight was normal. A more unique finding was that those that had been <2.5 kg at birth (growth restricted?) also manifested a significantly increased risk of DM during pregnancy. Although there remains debate about the mediation of this risk, the observations indicate that in humans, females with low birth weight may carry an increased risk for GDM.

The contrasts and similarities in the phenotypes of individuals with restricted growth (impaired nutrition) during intrauterine life and those exposed to maternal diabetes (over-nutrition) are striking and very interesting. This is illustrated in Table 4. As described above, the growth-restricted (impaired nutrition) group tends to be

small and lean as newborn infants and may experience what is called 'catch-up' growth and weight gain in childhood. By contrast, the offspring of mothers with diabetes (ODM) or GDM (over-nourished) tend to be heavy (with increased body fat content) at birth and later show a pattern of slower ('catch-down') growth during infancy.<sup>[16,27]</sup> Obesity tends to appear during pre-adolescence and puberty in both groups. The offspring of mothers with DM remain at risk for obesity, IGT/DM and GDM. The same may be true, but as yet unproven, in the intrauterine growth restricted group. Increased risks of obesity, cardiovascular disease and overt diabetes mellitus were found in the initial growth restricted cohort. The risks have not been fully determined in those exposed to maternal DM or GDM. The nature of the 'programming' that occurs with growth restriction or maternal diabetes to convey the propensities to obesity and altered glucose homeostasis in offspring remains to be determined.

### Summary

Genetic factors contribute importantly to obesity and type 2 DM; however, the epidemic increases that are occurring in both disorders are being driven by environmental factors. The intrauterine exposure to an altered metabolic environment, be it under-nutrition (growth restriction) or over-nutrition (maternal diabetes), represents one important contributing environmental factor. In the case of diabetes, the transgenerational appearance of obesity and altered glucose homeostasis can be viewed as a self-sustaining, vicious cycle.

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**Table 4: Contrasts in development after exposure to 'reduced'\* or 'excess'\*\* nutrients during intrauterine development**

|             | Growth restricted              | Mother with DM or GDM            |
|-------------|--------------------------------|----------------------------------|
| At birth    | Small, lean newborn            | Increased weight and adiposity   |
| Child       | Early "catch-up" growth/weight | Early "catch-down" growth/weight |
| Adolescent  | Obesity + IGT/DM (?)           | Obesity and IGT/DM               |
| Young adult | Obesity + GDM (?)              | Obesity + GDM/DM                 |
| Older adult | Obesity + CVD + IGT/DM         | Obesity + IGT/DM + CVD (?)       |

\*It is inferred that growth-restricted fetus/newborn experienced reduced or impaired nutrient delivery, \*\*It is inferred that fetus/newborn of mother with DM or GDM received excess nutrient delivery, IGT - Impaired glucose tolerance, DM - Diabetes mellitus, GDM - Gestational diabetes mellitus, CVD - Cardiovascular disease

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**Source of Support:** Nil, **Conflict of Interest:** None declared.