Determinants of Incident Hyperglycemia 6 Years After Delivery in Young Rural Indian Mothers

The Pune Maternal Nutrition Study (PMNS)

SMITA R. KULKARNI, MSC[1]
CAROLINE H.D. FALL, DM, FRCPCH[2]
NIRANJAN V. JOSHI, MD, DNB[1]
HIMANGI G. LUBREE, MSC[1]
VAISHALI U. DESHPANDE, MSC[1]
RASHMI V. PASARKAR, MSC[1]
DATTATRAY S. BHAT, MSC[1]
SADANAND S. NAIK, PHD[1]
CHITTARANJAN S. YAJNIK, MD, FRCP[1]

OBJECTIVE — To study determinants of incident hyperglycemia in rural Indian mothers 6 years after delivery.

RESEARCH DESIGN AND METHODS — The Pune Maternal Nutrition Study collected information in six villages near Pune on prepregnant characteristics and nutrition, physical activity, and glucose tolerance during pregnancy. An oral glucose tolerance test (OGTT) was repeated 6 years after delivery.

RESULTS — A total of 597 mothers had an OGTT at 28 weeks' gestation; 3 had gestational diabetes (by World Health Organization 1999 criteria). Six years later, 42 of 509 originally normal glucose-tolerant mothers were hyperglycemic (8 diabetic, 20 with impaired glucose tolerance, and 14 with impaired fasting glucose). The hyperglycemic women had shorter legs and thicker skinfolds before pregnancy ($P < 0.01$, both), were less active and more hyperglycemic (2-h plasma glucose 4.8 vs. 4.4 mmol/l, $P < 0.001$) during pregnancy, and gained more weight during follow-up (6.0 vs. 2.7 kg, $P < 0.001$). Multivariate analysis revealed that total leukocyte count and blood pressure during pregnancy were additional independent predictors of 2-h glucose concentration at follow-up.

CONCLUSIONS — Our results suggest that compromised linear growth, adiposity, inflammation, and less physical activity predispose to hyperglycemia in young rural Indian women. International cut points of diabetes risk factors are largely irrelevant in these women.

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India has the largest number of diabetic patients in any one country (1) and has been called the "diabetes capital" of the world. Risk factors for diabetes in Indians are mostly derived from cross-sectional surveys (2); there are only a few prospective studies of incident diabetes (3). Classic risk factors for type 2 diabetes include a family history of diabetes, higher age, greater obesity (total and central), and insulin resistance. Recent research has revealed a role for new genetic markers (4), adverse intrauterine environment and accelerated childhood growth (5), inflammation (6), and endothelial dysfunction (7). Interestingly, short height and short legs have also been associated with risk of type 2 diabetes (8).

From the [1]Kamalnayan Bajaj Diabetology Research Centre, KEM Hospital and Research Centre, Pune, India; and the [2]MRC Epidemiology Resource Centre, University of Southampton, Southampton, U.K.

Address correspondence and reprint requests to Dr. Chittaranjan Sakerlal Yajnik, MD, FRCP, KEM Hospital and Research Center, 6th Floor, Banoo Coyaji Building, Sardar Mudliar Road, Rasta Peth, Pune 411011, India. E-mail: diabetes@vsnl.com.

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Abbreviations: GDM, gestational diabetes mellitus; IFG, impaired fasting glycemia; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; PMNS, Pune Maternal Nutrition Study; SES, socioeconomic status; TLC, total leukocyte count.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

There is growing recognition that pregnancy is a window revealing future metabolic and cardiovascular risk for the mother (9). Hormonal, metabolic, and inflammatory stresses of pregnancy unmask underlying susceptibility to diabetes. The original definition of gestational diabetes mellitus (GDM) was based on the level of glycemia that predicts future risk of diabetes (10). Over two-thirds of GDM women in our clinic were hyperglycemic within 4 years of delivery (11), one of the highest rates anywhere. There is little community-based information in India on the predictive value of measurements during pregnancy for future risk of diabetes.

The Pune Maternal Nutrition Study (PMNS) is a community-based study of maternal nutrition, metabolism, and fetal growth in six villages near Pune, Maharashtra, India (12). Women were enrolled before pregnancy, and during pregnancy, anthropometric, nutritional, and biochemical-metabolic measurements were made, including a 75-g oral glucose tolerance test (OGTT). The OGTT was performed 6 years after delivery, providing an opportunity to study risk factors in pregnancy for future hyperglycemia.

RESEARCH DESIGN AND METHODS

— The study design and methods of the PMNS have been described (12). We identified 2,675 married nonpregnant women for possible enrolment, and 2,466 agreed to participate. Field workers recorded menstrual dates, detailed anthropometry, and socio-economic status (SES) using a standardized questionnaire. Women missing two successive periods underwent an ultrasound examination; singleton pregnancies of <21 weeks' gestation were included.

Maternal measurements in pregnancy

At 18 ± 2 and 28 ± 2 weeks' gestation, we measured anthropometry and dietary intakes using a semi-weighted 24-h recall method and a food frequency questionnaire. A structured questionnaire was used to record typical daily routine, which included farming and domestic activities. Us-

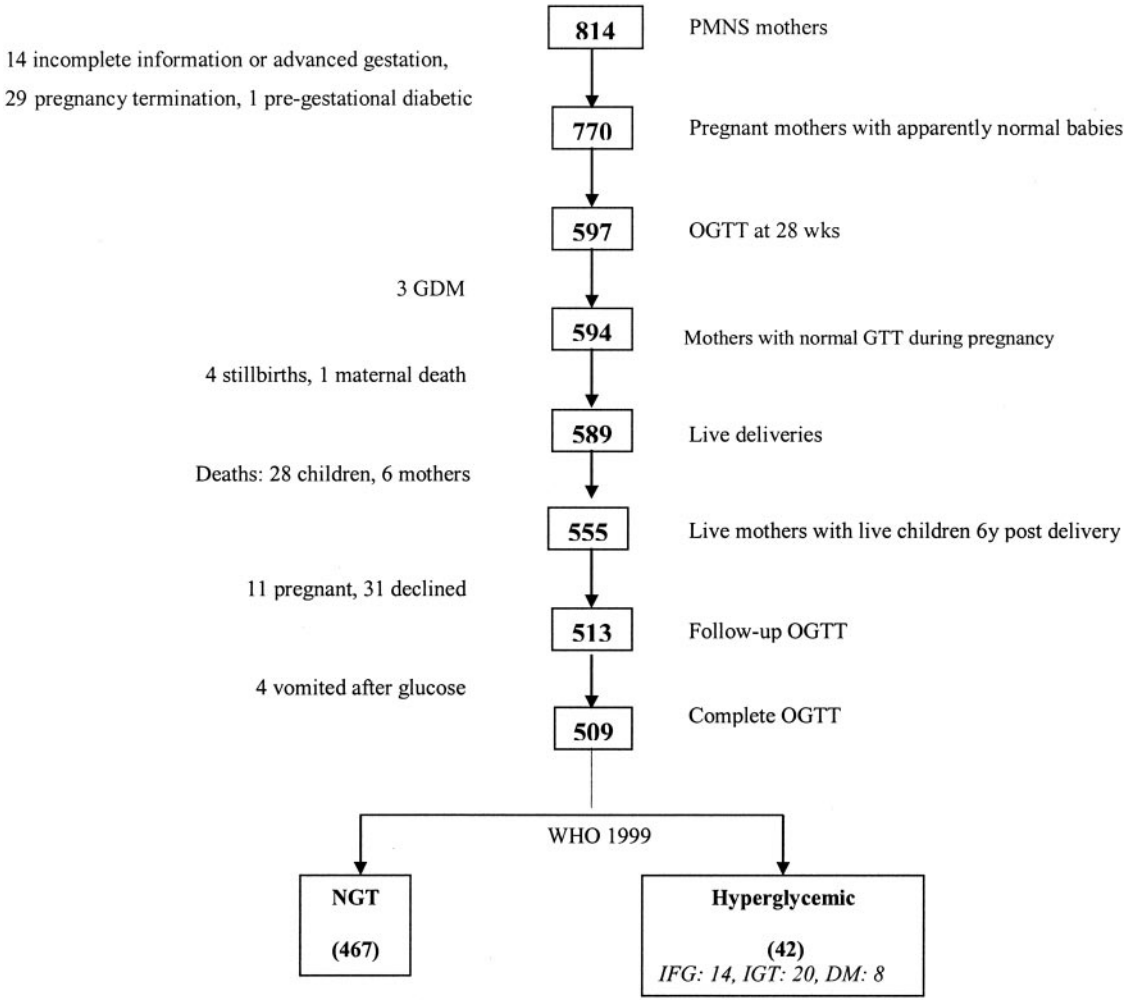

Figure 1—*Study subjects. DM, diabetes; GTT, glucose tolerance test; NGT, normal glucose tolerance; WHO, World Health Organization.*

ing published data on the energy cost of various activities, a weighted total daily score was derived (13). At 28 weeks, an OGTT (75-g anhydrous glucose) was performed and venous blood samples obtained fasting and 2-h postglucose.

Blood measurements included hemoglobin, total leukocyte count (TLC), platelet count (Beckman Coulter T540), plasma glucose, total cholesterol, and triglyceride concentrations using standard kits and insulin, proinsulin, and 32–33 split proinsulin using a Delfia assay. Insulin resistance was calculated from the homeostasis model assessment equation (14). Glucose tolerance was classified by World Health Organization 1999 criteria (15). At delivery, we made detailed measurements of the baby's size. Enrollment started in June 1994, and the last delivery occurred in November 1996.

Maternal measurements at 6-year follow-up

The women were invited for an OGTT 6 years after delivery (2000–2002). They arrived the evening before, were given a standard dinner, and rested overnight (only water by mouth). A 75-g OGTT was carried out next morning. Information on medical events and pregnancies since the index delivery was recorded by trained medical officer using a questionnaire. Anthropometric measurements included height and sitting height to the nearest 1 mm using a Harpenden stadiometer. Blood pressure was recorded in the supine position using an automated machine (UA 767PC; A and D Instruments, Abingdon, Oxford, U.K.). SES before pregnancy was assessed using the Kuppuswamy score (16) and at the 6-year follow-up using the National Family Health Survey-2 standard of living index (17).

Definitions and calculations

Impaired fasting glycemia (IFG), impaired glucose tolerance (IGT), and diabetes were diagnosed per World Health Organization 1999 criteria (15). Metabolic syndrome was defined using International Diabetes Federation 2006 criteria (18). Fat mass was calculated from four skinfolds by Durnin's method (19) and leg length by subtracting sitting height from total height. Preterm birth was defined as a delivery before 37 weeks' gestation. Babies weighing <2,500 g at birth were defined as having low birth weight. Babies with weight above the gestation and sex-specific 90th percentile were defined as large for gestational age and those below the 10th percentile as small for gestational age. Adverse fetal outcome was defined as a history of any of the following: two or more spontaneous abortions, a stillbirth, neonatal death, or preterm delivery.

Ethical permission for the study was granted by the KEM Hospital Ethical Committee and by the local village leaders. The women signed written informed consent.

Statistical methods

Data are presented as means ± SD. Variables with skewed distributions (subscap-

Table 1—*Anthropometric and biochemical characteristics of the mothers at follow-up (6 years after the index pregnancy) according to current glycemic status (by World Health Organization 1999 criteria)*

	Normoglycemic	Hyperglycemic	*P*	*P**
n	467	42		
Age (years)	27.9 ± 3.5	28.6 ± 4.5	0.258	—
Completed secondary school	330 (53.6)	39 (68.4)	0.128	—
Upper SES (upper quartile of score)	180 (31.4)	18 (36.7)	0.694	—
Deliveries after index delivery	1.6 ± 0.9	1.7 ± 0.9	0.671	0.525
Weight (kg)	44.4 ± 6.9	47.7 ± 8.9	0.004	0.026
Height (cm)	152.1 ± 5.0	150.4 ± 4.4	0.040	0.063
Leg length (cm)	73.5 ± 3.9	71.4 ± 4.5	0.001	0.001
BMI (kg/m^2)	18.9 ± 2.6	20.9 ± 3.8	0.0001	0.0001
Waist (cm)	65.6 ± 6.9	70.3 ± 11.1	0.0001	0.002
Hip (cm)	85.4 ± 6.8	88.6 ± 10.1	0.012	0.028
Waist-to-hip ratio	0.77 ± 0.06	0.79 ± 0.09	0.010	0.043
Sum of four skinfolds (mm)	37.1 ± 17.6	49.4 ± 25.1	0.0001	0.0001
Body fat % (from four skinfolds)	22.0 ± 5.8	25.2 ± 7.3	0.001	0.003
Weight gain prepregnancy to 6-year follow-up (kg)	2.7 ± 5.1	6.0 ± 6.8	0.0001	0.0001
Fat mass gain prepregnancy to 6-year follow-up (kg)	1.2 ± 3.5	2.9 ± 4.5	0.004	0.007
Fasting plasma glucose (mmol/l)	5.1 ± 0.5	6.2 ± 1.8	0.0001	0.0001
2-h plasma glucose (OGTT) (mmol/l)	5.2 ± 1.1	8.8 ± 3.4	0.0001	0.0001
Fasting plasma insulin (pmol/l)	35.4 ± 34.0	37.5 ± 24.3	0.701	0.620
Insulin resistance (HOMA-IR)	0.65 ± 0.56	0.77 ± 0.52	0.129	0.150
Blood pressure (mmHg)	107/64 ± 9/7	115/68 ± 10/7	0.0001	0.0001
Plasma total cholesterol (mmol/l)	3.6 ± 0.7	3.8 ± 0.7	0.168	0.402
Plasma HDL cholesterol (mmol/l)	1.2 ± 0.3	1.2 ± 0.3	0.363	0.385
Plasma triglycerides (mmol/l)	0.7 ± 0.3	1.0 ± 1.4	0.0001	0.0001
TLC ($\times 10^9$/l)	7.2 ± 1.6	7.8 ± 2.1	0.045	0.053
Metabolic syndrome (IDF 2005 criteria)	7 (1.2)	8 (15.4)	0.0001	—

Data are *n* (%) and means ± SD. *Statistical significance after adjusting for maternal age and SES at the time of the measurements, by ANOVA. HOMA-IR, homeostasis model assessment of insulin resistance; IDF, International Diabetes Federation.

ular and triceps skinfold thickness and maternal insulin concentrations) were log transformed to satisfy assumptions of normality. Pearson correlation coefficients were used to study associations. Multiple linear and logistic regression and ANOVA models were used to assess whether associations were independent of potential confounding factors. Analyses were carried out using STATA (version 7.0).

RESULTS — Of 814 pregnancies enrolled in the PMNS, 770 mothers delivered normal, live, single babies. A total of 597 women had an OGTT. Three were diagnosed with GDM and excluded from the analysis of incident hyperglycemia. Of 594 normal glucose-tolerant mothers, 4 who delivered stillbirths and 28 whose children died were not followed up; 7 mothers died, 11 were pregnant, and 31 declined to participate. Thus, an OGTT was performed on 513 nonpregnant mothers: 4 vomited, and 509 completed the test (94% of eligible). Fourteen mothers were classified as IFG, 20 as IGT, and 8 as diabetic; together they are referred to as hyperglycemic and the rest as normoglycemic ($n = 467$) (Fig. 1). Women who did not have an OGTT during pregnancy ($n = 173$) and those who were not followed up did not differ in age, BMI, and SES compared with those who were studied.

Characteristics of the women at 6-year follow-up

Hyperglycemic women were of similar age, SES, and parity compared with normoglycemic women (Table 1). None of these women reported a first-degree relative with diabetes. Hyperglycemic women were shorter, heavier, and had higher BMI, higher waist and hip circumferences and waist-to-hip ratios, thicker skinfolds, and higher percentages of body fat. Their shorter height was mostly accounted for by shorter legs. Hyperglycemic women gained more weight over the period of the study and had higher blood pressure, fasting plasma triglyceride concentrations, and TLC. Fasting plasma insulin concentrations and homeostasis model assessment of insulin resistance were similar in the two groups. Fifteen percent of the hyperglycemic and 1% of the normoglycemic women had the metabolic syndrome.

Prepregnancy and pregnancy characteristics

Hyperglycemic women reported a larger number of adverse fetal outcomes (mostly abortions) but had similar parity (Table 2). They had larger skinfolds and marginally higher percentages of body fat and waist circumference.

At 28 weeks' gestation, the subsequently hyperglycemic women had higher 2-h plasma glucose concentrations (by OGTT) and higher blood pressure; other biochemical and hematological measurements were similar in the two groups. Macronutrient intake; frequencies of intake of green leafy vegetables, fruit, and milk; and circulating concentrations of vitamin B12, folate, vitamin C, and homocysteine were similar in the two groups (data not shown).

As a group, these women had high levels of physical activity. Domestic work included cooking, washing clothes and utensils, and fetching water and firewood. Farming activities included taking care of

Table 2—*Maternal characteristics before and during the index pregnancy according to glycemic status at 6-year follow-up*

	Normoglycaemic	Hyperglycemic	*P*	*P**
n	467	42		
Prepregnancy				
Adverse fetal outcome (%)	24 (5.2)	8 (19.0)	0.0001	—
Parity	1.2 ± 1.2	1.3 ± 1.3	0.630	0.837
Tobacco use (%)	132 (28.3)	4 (9.5)	—	—
Weight (kg)	41.7 ± 4.9	41.6 ± 6.9	0.950	0.991
BMI (kg/m^2)	18.0 ± 1.8	18.4 ± 2.8	0.232	0.261
Waist (cm)	60.5 ± 5.4	62.2 ± 8.5	0.069	0.075
Hip (cm)	81.4 ± 4.9	82.0 ± 6.5	0.465	0.514
Waist-to-hip ratio	0.74 ± 0.06	0.76 ± 0.08	0.180	0.179
Sum of four skinfolds (mm)	33.8 ± 12.3	38.7 ± 18.1	0.018	0.028
Body fat % (from four skinfolds)	20.9 ± 4.2	22.4 ± 5.4	0.044	0.071
28 weeks' gestation				
Hemoglobin (g/l)	112.0 ± 15.0	114.0 ± 12.0	0.363	0.279
Fasting plasma glucose (mmol/l)	3.9 ± 0.6	4.1 ± 0.8	0.180	0.178
2-h plasma glucose (OGTT) (mmol/l)	4.4 ± 1.0	4.8 ± 1.4	0.008	0.009
Fasting plasma insulin (pmol/l)	23.5 ± 37.9	20.6 ± 14.1	0.635	0.531
Pro-insulin (pmol/l)	2.5 ± 2.1	2.5 ± 1.9	0.983	0.992
32–33 split pro-insulin (pmol/l)	3.4 ± 4.4	3.2 ± 2.7	0.812	0.885
Pro-insulin–to–insulin ratio	0.21 ± 0.33	0.15 ± 0.12	0.273	0.288
Insulin resistance (HOMA-IR)	0.78 ± 1.1	0.73 ± 0.57	0.770	0.641
Blood pressure (mmHg)	112/62 ± 9/8	115/64 ± 9/3	0.055	0.078
Plasma total cholesterol (mmol/l)	4.8 ± 0.9	4.9 ± 0.8	0.713	0.652
Plasma HDL cholesterol (mmol/l)	1.1 ± 0.3	1.1 ± 0.3	0.224	0.190
Plasma triglycerides (mmol/l)	1.5 ± 0.5	1.6 ± 0.7	0.282	0.323
TLC ($\times 10^9$/l)	9.1 ± 1.9	9.5 ± 2.5	0.286	0.282
Macro nutrient intake/day				
Total energy (kcal)	1,690.8 ± 498.3	1,623.4 ± 441.8	0.408	0.753
Protein (g)	44.1 ± 13.9	42.9 ± 12.5	0.598	0.991
Fat (g)	32.6 ± 13.8	31.9 ± 11.9	0.747	0.914
Carbohydrate (g)	304.9 ± 89.8	290.0 ± 80.5	0.311	0.591
Activity scores				
Total	65.7 ± 25.3	51.8 ± 24.6	0.001	0.003
Domestic	28.7 ± 13.2	23.3 ± 17.6	0.019	0.031
Farming	27.2 ± 15.7	23.3 ± 16.5	0.295	0.348
At delivery				
Preterm delivery (%)	60 (9.7)	5 (8.6)	0.507	—
Caesarean section (%)	21 (4.5)	2 (4.8)	0.986	—
Birth weight (g)†	2,646 ± 363	2,628 ± 425	0.775	0.709
Birth weight <2,500 g (%)	172 (38.0)	13 (33.0)	0.519	—
Birth weight >90th centile (LGA) (%)	35 (7.9)	4 (10.3)	0.599	—
Birth weight <10th centile (SGA) (%)	44 (9.9)	5 (12.8)	0.560	—

Data are *n* (%) and means ± SD. *Statistical significance after adjusting for maternal age and socioeconomic status at the time of the measurements, by ANOVA. †Birth weight adjusted for gestation and sex. HOMA-IR, homeostasis model assessment of insulin resistance; LGA, large for gestational age; SGA, small for gestational age.

animals, milking animals, and farm labor. The hyperglycemic women had a lower physical activity score than the normoglycemic women due to lower domestic activity.

None of the PMNS women smoked. Ten percent ($n = 4$) of hyperglycemic women and 28% of normoglycemic women either chewed tobacco or used it as tooth powder (Mishri).

Birth weight and other anthropometric measurements of the newborns were similar in the two groups of women, as were the rates of low birth weight, small for gestational age, large for gestational age, and preterm delivery.

Multivariate associations of 2-h plasma glucose concentration and incident hyperglycemia at 6 years

We analyzed the associations of glycemic status at follow-up by two methods: *1*) using 2-h plasma glucose concentration as a continuous variable and *2*) using incident hyperglycemia (IFG + IGT + diabetes) as a categorical variable (Table 3 and online appendix Table 3*B* [available at http://dx.doi.org/10.2337/dc07-0329]).

Multiple linear regression analysis showed that higher 2-h plasma glucose concentration was associated with shorter legs and higher prepregnant fat mass, 2-h plasma glucose concentration, TLC, systolic blood pressure during pregnancy, and weight gain over 6 years. Age, SES, parity, prepregnant waist circumference, physical

Table 3—*Multiple linear regression analysis of predictors of 2-h plasma glucose concentrations during the OGTT 6 years after delivery and multiple logistic regression analysis of predictors of incident hyperglycemia (IFG + IGT + diabetres, World Health Organization 1999 criteria) 6 years after delivery*

	Predictors of 2-h glucose			Predictors of incident hyperglycemia		
	β	95% CI	*P*	OR	95% CI of OR	*P*
Age (years)	0.037	0.0272–0.0468	0.554	0.911	0.776–1.071	0.259
SES	0.046	0.0421–0.0499	0.360	0.967	0.909–1.029	0.295
Parity	−0.010	−0.0394 to 0.0194	0.877	1.321	0.822–2.125	0.250
Prepregnant						
Leg length (cm)	−0.120	−0.1259 to −0.1141	0.019	0.875	0.802–0.954	0.003
Waist circumference (cm)	0.038	−0.0321 to 0.0439	0.534	1.014	0.926–1.110	0.764
Fat mass (kg)	0.161	0.1473–0.1747	0.014	1.140	0.955–1.361	0.148
At 28 weeks' gestation						
Physical activity	−0.030	−0.0319 to −0.0280	0.561	0.974	0.954–0.995	0.014
2-h glucose (mmol/l)	0.112	0.1100–0.1139	0.023	1.011	0.991–1.031	0.296
Fasting insulin (pmol/l)	0.036	0.0340–0.0379	0.454	0.991	0.966–1.016	0.469
TLC ($\times 10^9$/l)	0.112	0.0983–0.1257	0.021	1.083	0.907–1.294	0.378
Systolic blood pressure (mmHg)	0.098	0.0960–0.0999	0.047	1.025	0.982–1.069	0.261
At delivery						
Birth weight of child (g) (gestation and sex adjusted)	−0.066	−0.0954 to −0.0366	0.188	0.738	0.482–1.131	0.163
Weight gain prepregnancy to follow-up (kg)	0.160	0.1541–0.1659	0.001	1.064	0.998–1.134	0.057

activity, plasma insulin concentrations during pregnancy, and birth weight of the child were not significantly associated in this analysis. Replacing prepregnant fat mass by BMI revealed that BMI was not related.

To assess the relative significance of the association of independent variables with 2-h plasma glucose concentration, we performed stepwise regression analysis, which serially selects the independent variable most correlated with the dependent variable while controlling for those already selected, and the process is repeated until the newly added variable fails to make a significant contribution to variance. The results are shown in online appendix Table 3*B*. The contribution was 2.3% for weight gain, followed by prepregnant fat mass (2.6%), leukocyte count (1.4%), 2-h glucose (1.5%), and systolic blood pressure (0.9%) at 28 weeks' gestation. Age, SES score, parity, prepregnant waist circumference, physical activity and fasting insulin at 28 weeks' gestation, and birth weight of child and leg length of the mother were not contributory.

Logistic regression analysis showed that incident hyperglycemia was predicted by shorter leg length and lower physical activity during pregnancy. Age, SES, parity, prepregnant waist circumference, fat mass, 2-h glucose concentration and plasma insulin concentrations, TLC, blood pressure during pregnancy, and birth weight of the child were not significant predictors in this analysis. The results were very similar when the incident hyperglycemia was restricted to IGT + diabetes.

CONCLUSIONS — This is the first community-based study in India to report on incident hyperglycemia in rural women. Eight percent of these young women developed fasting or postglucose hyperglycemia between 21 and 28 years of age. Hyperglycemic women were shorter (especially in the legs) and more adipose from prepregnancy, and at the time of diagnosis had higher BMI, waist circumference, waist-to-hip ratio, and percentage of body fat than the normoglycemic women. However, by international standards, many of these women were underweight and thin: of the hyperglycemic women, 26 (62%) had a BMI <18.5 kg/m^2 prepregnancy and 14 (33%) at the time of diagnosis of hyperglycemia. Our results support the previous finding that the thin-fat phenotype predisposes to type 2 diabetes (20). It is also clear that the international cut points for obesity and central obesity are inappropriate in young rural Indian women. The recently suggested cut point of BMI for obesity-related public health action in Asians (23 kg/m^2) (21) also seems far too high for these rural Indian women.

In our study, shortness and fatness independently predicted higher glycemia, and the short and fat women were the most hyperglycemic. Short stature reflects a deficit in linear growth in early life, contributed both by genetic and nutritional factors; it is a risk factor for GDM, type 2 diabetes, hypertension, and coronary heart disease (8,22,23). Short legs represent a caudal diminution of growth and may represent intrauterine programming of body proportions. Increasing adiposity in a short individual reflects a rapid nutritional transition and increases the risk of type 2 diabetes, even in young rural Indian women.

A number of measurements during pregnancy were predictive of later hyperglycemia. These included higher postglucose glycemia, higher blood pressure, and higher TLC (all within the "normal" range). The plasma glucose concentrations during the pregnancies of subsequently hyperglycemic women were far below currently used cut points for diagnosis of GDM, suggesting that the gradient of risk may be very steep in susceptible populations. Higher glycemia was associated with higher TLC in pregnancy and at follow-up, suggesting an association with inflammation. TLC and other inflammatory markers are predictive of incident diabetes in Pima Indians, as shown in the Atherosclerosis Risk in Communities study (24,25). "Inflammation" could reflect heightened "innate" immunity (6). However, in pregnancy, it could be a maternal response to the conceptus (26), and the placenta secretes a number of proin-

flammatory cytokines (interleukin-6, tumor necrosis factor-α, leptin, etc.) (27). Association between higher blood pressure and hyperglycemia could reflect endothelial dysfunction, which also contributes to type 2 diabetes susceptibility (7). Thus, our results suggest that metabolic, inflammatory, and vascular changes in pregnancy predict future hyperglycemia and support the concept that pregnancy is a window on future health and disease.

Incident hyperglycemia (IFG + IGT + diabetes) was predicted by short legs, lower physical activity during pregnancy, and higher weight gain. In this farming community, physical activity during pregnancy is a surrogate of habitual physical activity, which is quite high. The typical daily activity of the hyperglycemic women far exceeds the current recommendations for physical activity to prevent diabetes (150 min walking per week) (28). Finally, weight gain predicted incident hyperglycemia. This is too well known and operates through increased insulin resistance.

Our study has many strengths. We made a wide range of measurements specifically designed to answer relevant hypotheses. The community participation and follow-up rates are high (>90%). The rural Indians represent 70% of India's population, who will contribute increasingly to the burgeoning epidemic of diabetes in India. Our findings therefore provide useful public health information for the policy makers. One weakness is that leg length was measured only at follow-up; however, it is fairly stable in young adults.

Our findings suggest possible interventions to reduce the incidence of diabetes in Indians. There is a need to take a "life-course" approach and include measures to promote skeletal and lean growth in early life, to promote physical activity, and to eliminate sources of chronic inflammation. In practical terms, active prevention of weight gain in people who are "thin" by the currently accepted norms will be a challenging task.

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