Gestational Blood Glucose Levels in Normal and Potentially Diabetic Women Related to the Birth Weight of Their Infants

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SUMMARY

Data from 5,534 prenatal registrants who had blood glucose determinations following the ingestion of 50 gm. of glucose indicated that age is the only maternal factor of significance to resulting blood glucose levels when other variables are held fixed.

The lack of a blood glucose—birth weight correlation in the general population was further explored with the demonstration that such a relationship exists among groups of potentially diabetic women.

Overweight women giving birth to a large baby were found to have significantly higher mean blood glucose values. The overweight women with an infant of average birth weight or the normal weight women with a large baby had no such blood glucose elevation. These data imply that more accurate separation of either the overweight women or women giving birth to large babies into groups of special significance to future development of diabetes mellitus is possible. DIABETES *15*:466-70, July, 1966.

Maternal hyperglycemia is believed to result in an increase in fetal insulin production. A consequent increase in fat deposition is considered responsible for the excessive weight of infants born to mothers with clinical and preclinical diabetes.[1-3] Data substantiating such a hypothesis are difficult to obtain since the prediabetic women are usually not identified until the completion of their pregnancies by the birth of large babies, fetal wastage or the subsequent development of diabetes. In known diabetics the role of treatment complicates the interpretation.

Blood glucose levels determined during pregnancy were available to us in over five-thousand patients. These data allow a correlation of birth weight with the blood glucose levels obtained during the same pregnancy. Due consideration is given to related influencing factors such as age, parity, maternal weight, length of gestation, and birth weight levels at which a baby is considered large, with a quantitative assessment of the separate effects of these various factors.

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MATERIAL AND METHODS

Data were obtained from all prenatal patients registering at the Boston City Hospital between Nov. 1, 1957 and Sept. 30, 1959. These 5,883 patients were questioned with regard to age, gestational age, usual weight, height, parity, and previous large babies (in excess of 9 lbs.). A venous blood sample in a fluoride tube was obtained one hour following oral ingestion of 50 gm. of glucose in a 50 per cent solution on the afternoon of registration. Blood glucose determinations were completed the same afternoon or the filtrate stage was prepared for completion on the following morning, using the technic of Somogyi-Nelson. The weights of the infants born during the study were recorded in the delivery room. A total of 5,534 patients remained after those who did not deliver at the hospital and those with multiple births or known diabetes were excluded from the 5,883 registrants. For descriptive purposes, infants weighing 9 lbs. or greater at birth are termed large babies. Gestational age in weeks at the time of delivery was calculated from the first day of the last menstrual period.

A 10 per cent subsample of the 5,534 patients was subsequently selected for special statistical handling. This was accomplished by selecting every tenth patient in order of registration. Among the sample of 553, a total of 513 women remained for study following the ex-

clusion of women registering prior to fourteen weeks gestation, incomplete pregnancies, and those whose height or weight was not recorded. Both simple and multiple linear regression technics were utilized when it was found that the statistical requirements of linearity of regression and homogeneity of variance were satisfactory for each independent variable studied in relation to the blood sugars.[4] The validity of the conclusions from the statistical handling of the subsample were checked by figures from the total population using three-way cross classification tables.

Potential diabetes is a term employed to designate individuals with an increased risk of future diabetes. For this presentation it is used to describe *persons giving birth to large babies, women who are 20 per cent or more in excess of their ideal weight* (Metropolitan Life Standards for Ideal Weight) and *individuals in the upper 5 per cent of the population's blood sugar distribution.*

RESULTS

An increase in the patient's age, parity, and number of previous large babies when studied separately is found to be associated with a significant rise in gestational blood glucose levels (table 1, simple regression). These findings, however, do not consider the effects of overlap among the variables. For example, an increase in parity must necessarily be accompanied by a rise in age and to which variable the corresponding rise in blood sugar should be attributed is uncertain. Isolation of the change in blood sugar associated with each individual factor can be achieved by using a multiple regression analysis. Such an analysis, in fact, indicates that the only factor of significance to the blood sugar level in pregnancy when all the variables are included is the patient's age (table 1, multiple regression). When examined by simple threeway cross classification tables, the actual glucose values for the total study population (5,534 persons) are in general agreement with these results of regression analyses.

The possibility that a significant relationship between blood glucose and birth weight is in operation in those women giving birth to large babies was considered. The small number of patients in this category might have allowed such a finding to be obscured by the rest of the group. Multiple regression analyses confined to such special groups of women considered to be potentially diabetic were, therefore, undertaken. When the data are confined to the 213 patients with current deliveries of infants in excess of 9 lbs., age and birth weight were significantly related to maternal blood glucose ($P < .001$, $P < .05$ respectively). Similar conclusions were obtained with the data restricted to women whose blood glucose levels were in the upper 5 per cent of the population of 5,534 persons (Age $P < .001$, birth weight $P < .001$). Finally, confining the analysis to those women who were 20 per cent or more above their ideal weight revealed that age, birth weight (6 lbs. or greater), and a history of having borne a large baby were all significantly related to maternal blood glucose ($P < .001$, $P < .01$, $P < .05$ respectively). The interrelations among these results were subsequently explored by studying the findings in overweight women giving birth to large babies.

Table 2 depicts the special relationship of maternal blood glucose to the birth of a large baby in relation to the mother's weight. The results demonstrate the expected higher average gestational blood glucose levels in

TABLE 1

Variables affecting blood sugar*
Simple and multiple linear regression analyses on 513 pregnant women

Variable	Blood sugar coefficients: Simple regression (mg. per 100 ml.)	Blood sugar coefficients: Multiple regression (mg. per 100 ml.)	Degree of importance (B)†
Age	.95 mg. per year‡	.84 mg. per year‡	.202
Per cent over ideal weight	.07 mg. per per cent weight	.02 mg. per per cent weight	.015
Current birth weight	—.06 mg. per ounce	—.08 mg. per ounce	.060
Number of previous pregnancies	1.73 mg. per previous pregnancy‡	.10 mg. per previous pregnancy	.009
Week of gestation at screening	.23 mg. per week	.16 mg. per week	.042
Large baby history	5.94 mg. if present§	3.42 mg. if present	.057

*One hour following 50 gm. of glucose administered orally during pregnancy.
†This figure allows estimation of the relative degree of importance of each variable. Beta as a measure ranges from zero to one.
‡Statistically significant ($P < .01$).
§Statistically significant ($P < .05$).

TABLE 2

Blood sugar by current birth weight and maternal weight status

Current infant birth weight	Maternal weight	Mean blood sugar	Median blood sugar	Mean age	Mean per cent weight	Number
6 lbs. to 6 lbs. 15 ozs.	≦—10 per cent	101.4	99.0	23.0	—15.5	457
	Between ± 10 per cent	98.2	95.0	23.9	— 1.1	757
	10-19 per cent	104.8	101.0	26.0	14.1	192
	≧ 20 per cent	106.0	104.0	27.1	36.2	197
	TOTAL	100.9	98.0	24.3	1.2	1,603
7 lbs. to 7 lbs. 15 ozs.	≦—10 per cent	102.4	99.0	23.2	15.4	358
	Between ± 10 per cent	101.5	99.0	23.8	— 0.6	756
	10-19 per cent	103.3	100.5	26.2	13.9	200
	≧ 20 per cent	106.6	104.0	28.0	37.4	288
	TOTAL	102.9	100.0	24.7	4.7	1,602
8 lbs. to 8 lbs. 15 ozs.	≦—10 per cent	102.3	99.0	23.3	—15.0	104
	Between ± 10 per cent	106.0	103.0	25.1	0.1	317
	10-19 per cent	104.1	101.0	26.2	14.2	92
	≧ 20 per cent	113.7	110.0	28.5	41.6	181
	TOTAL	107.2	105.0	25.9	10.5	694
9 lbs. and greater	≦—10 per cent	104.2	101.0	22.4	—13.7	16
	Between ± 10 per cent	101.0	96.0	24.9	0.0	64
	10-19 per cent	115.5	116.0	28.2	14.4	35
	≧ 20 per cent	118.4	120.0	29.5	43.3	98
	TOTAL	111.6	108.0	27.3	21.1	213

patients giving birth to infants weighing 9 lbs. or more as compared with those whose infants are from 6 lbs. to 8 lbs. 15 ozs. The higher blood sugars in the mothers of large babies can be explained largely by the fact that they are found in older women. Within each birth weight grouping, it can be seen that the rise in average blood glucose levels with increasing maternal weight is also associated with increasing age. What is noteworthy, however, is the disproportionately higher mean blood sugar occurring in mothers who are 20 per cent in excess of their ideal weight when their pregnancy results in the birth of a baby weighing 9 lbs. or more. It can also be seen that two marginal groups also have unaccountably higher mean blood glucose levels — the women 20 per cent or more overweight giving birth to an 8 lb.-baby and the 10 to 19 per cent overweight mothers giving birth to infants weighing 9 lbs. and greater.

Finally, the significance of having previously given birth to a large baby was examined. Women with a history of having delivered a large baby have higher mean blood glucose levels during a subsequent pregnancy regardless of its outcome in terms of birth weight. The regression analyses attribute this primarily to the age difference of the groups. Nevertheless, when examined in terms of the weight of the mother, significant findings appear as illustrated in figure 1. Overweight women with

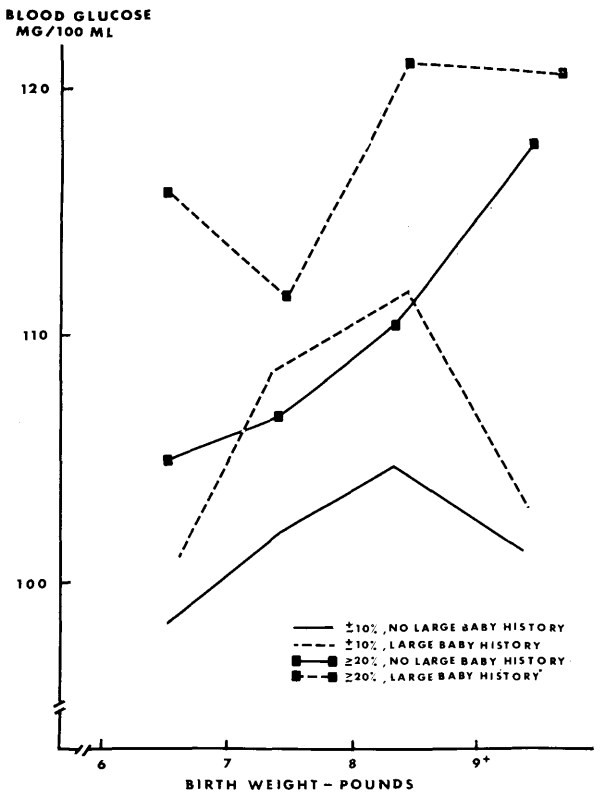

FIG. 1. Gestational blood glucose levels related to the birth weight outcome of the same pregnancy for women with and without a previous history of a large baby.

a history of a large baby have higher blood glucose levels regardless of the outcome of the current pregnancy. Overweight women without a history of a large baby exhibit similar blood glucose levels only when they are giving birth to a large baby for the first time. On the other hand, the women of normal weight with or without a history of a large baby have mean blood sugars which are significantly lower.

DISCUSSION

When such obvious variables as length of gestation are held constant, earlier data have indicated that the remaining factors of significance to birth weight are the previous birth of a large baby and maternal weight.[5] In this study of the possible conditions affecting gestational blood glucose levels, maternal age was the only one of importance when the other factors were held fixed. The commonly reported finding of higher blood sugars and heavier births associated with the mother's age and parity can thus be explained. As parity increases, birth weight increases due to the associated increase in maternal weight.[5] While parity itself has no effect on the mother's blood glucose level, a rise in parity is accompanied by an increase in age which in turn produces the effect reflected by the higher blood glucose levels.

The lack of any direct relationship between blood glucose in pregnancy and the subsequent weight of the infant does not apply to the whole range of birth weights. Different relationships are found to be operating in persons giving birth to large babies and other subgroups of women who may be termed potential diabetics. The blood sugar-birth weight mechanism that has been postulated for diabetics,[2] therefore, does operate in the prediabetic. The absence of evidence for such a mechanism in the whole population may be related to the persistent loss of glucose to the fetus reflected among other biochemical changes, by the fasting blood sugar levels which are lower antepartum than postpartum in normal pregnancies.[6] The further finding of significantly higher mean gestational blood sugar levels in overweight women giving birth to large babies implies that a nutritional abundance in these women allows an environmental explanation for the size of the infants. Conversely, the normal or underweight women having large babies were found to have significantly lower mean blood sugar levels, thereby implying alternative mechanisms, perhaps genetic, to be operating in this group. The overweight women not having large babies also had significantly lower blood sugar levels. It is tempting to compare this situation with animal experiments which isolate particular subgroups among the obese with differing metabolic behavior such as those with the obese-hyperglycemic syndrome.[7] The evidence that overweight women or persons giving birth to large babies might be readily classified into significant subgroups offers interesting possibilities for future study.

The birth of a large baby has been shown to have a certain predictive value in regard to future maternal diabetes.[8] Examining individuals with a history of a large baby should be profitable in discovering prediabetes, subject to the restrictions of such hearsay data. The absence of a significant blood glucose elevation in these persons is, however, an apparent denial of the predictive value of the large baby, since elevated blood glucose levels in pregnancy are directly related to future diabetes.[9] Here again, however, data from the whole population mask the significance of the findings in the subgroup of overweight women who have a high risk of future diabetes mellitus. Data from such potential diabetics clearly indicate significantly higher gestational blood sugar levels ($P < .05$) in persons with a history of having previously given birth to a large baby. When these history data are examined by maternal weight groups, they are found to be in full accord with our observed data — re-emphasizing the fact that having borne a large baby is of particular importance in an obese woman.

While the birth of a large baby or the presence of obesity has at one time or another been given some degree of prominence with respect to predicting future diabetes, the degree of certainty has frequently been debated, particularly as far as the individual is concerned. In view of our findings, it is of special interest to note that the literature dealing with follow-up studies on persons giving birth to large babies has some degree of uniformity. The authors in each instance have been particularly impressed by the frequency of obesity among such persons who later became diabetic.[10-12] There is, therefore, associated evidence for accepting the importance of the combination of obesity, large babies, and elevated gestational blood glucose levels as a means of predicting future diabetes. Although the maternal and infant weight can readily be determined, accurate categorization of a person by a blood glucose level awaits further knowledge of the biologic variability of blood glucose. *While reflecting accurately the significance of changes within groups, mean blood sugars cannot be used to reveal specific information which would allow classification of the individual.* The facts do suggest, however, that groups in a preclinical phase of

diabetes mellitus can be identified with a greater degree of certainty — a finding with significant implications to both clinical research and preventive medicine.

ACKNOWLEDGMENT

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REFERENCES

[1] Osler, M.: Body water of newborn infants of diabetic mothers. Acta Endocr. (Kbh) *34*:261-76, 1960.

[2] Pedersen, J.: Diabetes and Pregnancy: Blood Sugar in Newborn Infants. Copenhagen, Danish Science Press, 1952, p. 230.

[3] Driscoll, Shirley G., Benirschke, Kurt, and Curtis, George W.: Neonatal deaths among infants of diabetic mothers. A.M.A. J. Dis. Childhood *100*:818-35, 1960.

[4] Ezekiel, Mordecai, and Fox, Karl: Methods of Correlation and Regression Analysis. New York, John Wiley and Sons, 1959.

[5] O'Sullivan, J. B., Gellis, S., and Tenney, B.: Aspects of birth weight and its influencing variables. Amer. J. Obstet. Gynec. 92:1023-29, 1965.

[6] Bleicher, S. J., O'Sullivan, J. B., and Freinkel, N.: The interrelationships among glucose, insulin, and free fatty acids in late pregnancy and postpartum. New Eng. J. Med. *271*: 866-72, 1964.

[7] Mayer, Jean: The obese hyperglycemic syndrome of mice as an example of "metabolic obesity." Amer. J. Clin. Nutr. *8*:712-18, 1960.

[8] Kriss, J. P., and Futcher, P. H.: Relation between infant birth weight and subsequent development of maternal diabetes mellitus. J. Clin. Endocr. *8*:380-89, 1948.

[9] O'Sullivan, J. B., and Mahan, C. M.: Criteria for the oral glucose tolerance test in pregnancy. Diabetes *13*:278-85, 1964.

[10] Fitzgerald, M. G., Malins, J. M., and O'Sullivan, D. J.: Prevalence of diabetes in women thirteen years after bearing a big baby. Lancet *1*:1250-52, 1961.

[11] Gilbert, J. A. L.: The association of maternal obesity, large babies, and diabetes. Brit. Med. J. *1*:702-04, 1949.

[12] Kritzer, Marton D.: The significance of the birth of a large baby. Med. Clin. N. Amer. *36*:1151-55, 1952.

Hypermetabolism and Undernutrition

Many children with congenital cardiac disease do not grow properly. In general the degree of growth failure, both in height and weight, is greater in seriously ill children, and many who have mild defects grow quite normally (A. Mehrizi and A. L. Drash, J. Pediat. *61*: 418, 1962).

The observation is often easy to make, a determination of the cause often difficult. Such is the situation in respect to growth failure in congenital heart disease. Many suggestions have been made. Anorexia is a common feature in many severely ill children, as it is in the adult whose heart is failing. Tissue anoxia is another possibility, since growth failure is more profound in infants and children who are cyanotic. Some adult patients are known to have abnormal losses of protein in the urine and gastrointestinal tract (J. G. Pittman and P. Cohen, New Engl. J. Med. *271*:403, 453, 1964).

Hypermetabolism has also been suggested as a cause. The recent report of M. H. Lees, J. D. Bristow, H. E. Griswold and R. W. Olmsted (Pediatrics *36*:183, 1965) presents a study of this phenomenon in infants with congenital heart disease.

Twenty-one infants, aged two days to nine months, were studied. They presented a variety of cardiac defects, including patent ductus arteriosus, septal defects, and transposition of the great vessels. Seven were cyanotic. Three had an associated chromosomal abnormality (trisomy 21). Twenty-one control infants in the same age range were also studied.

The measurements were made under light sedation in a controlled temperature room. Expired gas was collected over a timed period with the infant breathing room air. Analysis of the expired gas, and its volume, permitted a calculation of resting oxygen consumption at standard temperature and pressure, in terms of milliliters per minute per kilogram body weight.

The average value for the control infants was 7.3, with a standard deviation of 0.8. This is somewhat higher than that reported by others, and the authors ascribe the difference to environmental conditions.

The infants with heart disease showed varying degrees of growth failure, ranging from normal to 43 per cent of ideal weight. Eleven were 60 per cent or less of ideal weight. In this latter group, the average oxygen consumption was 10.9 ± 1.4 ml., clearly in excess of the normal children. The average for the ten better grown infants was comparable to the controls, namely 7.5 ± 2.0 ml. per minute per kilogram.

A correlation coefficient was determined between resting oxygen consumption and relative body weight. This

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