# Brittle Diabetes in Pregnancy

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SUMMARY

**In eight brittle diabetics the insulin requirement increased during successful pregnancies from 35 to 64 U./day (in 29 stable severe diabetics from 53 to 78 U./day). The within-day glycemic excursions were calculated as the mean of the three differences between four time points: fasting, one hour after breakfast, two hours after breakfast, and two hours after lunch. This parameter was constant throughout the pregnancy in nondiabetics (34-46 mg./100 ml.) and stable severe diabetics (55-72 mg./100 ml.). In brittle diabetics it dropped from 147 mg./100 ml. before the pregnancy and 153 mg./100 ml. at eight weeks to 85 mg./100 ml. at 36 weeks. The between-day variability was calculated as the mean glycemic difference between two successive days at the four points of time noted above. It was very low in nondiabetics (12-16 mg./100 ml.) and much higher in stable diabetics (49-53 mg./100 ml.). In brittle diabetics it decreased from 127 mg./100 ml. before pregnancy and 120 mg./100 ml. at eight weeks to 46-55 mg./100 ml. at 24-36 weeks. This shows that brittleness substantially decreased in the second half of pregnancy.** DIABETES *26*:926-30, October, 1977.

Brittle diabetes is characterized by irregular, unpredictable, quick changes of glycemia even when insulin dose, food intake, and exercise are kept constant. This inevitably results in poorer control of diabetes and higher mean daily blood glucose levels.

The outcome of diabetic pregnancies is directly related to the degree of control[1]—the higher the maternal glycemia, the higher the fetal glycemia and insulinemia and the higher the risk of perinatal loss. Since brittle diabetics have higher mean glycemia, it would be natural to expect higher perinatal loss in the group than in more stable patients. We could not find any reference to the subject in the available literature. In our subgroup of eight patients with long-standing brittle diabetes there was no perinatal fetal loss. Looking for the explanation of this, we came across the fact that brittle diabetics were much more stable and therefore easier to control in the second half of their pregnancies, as a result of which both their mean glycemic levels and the outcome of their pregnancies were not different from those in stable pregnant severe diabetics.

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## MATERIAL AND METHODS

### *The Definition of Brittle Diabetes*

The patients included in the study met the following criteria: (1) they were under our observation both before and after their pregnancies and were known to be well disciplined, cooperative, and reliable; (2) careful clinical and laboratory observations excluded the Somogyi effect as a cause of brittleness;[2] (3) the swings of their blood glucose level were utterly unpredictable; (4) the mean of their daily differences of glycemia was above 100 mg./100 ml. (see below).

We used two parameters of brittleness: (1) The mean of daily differences of blood glucose (MDD) was calculated in the following way: on two consecutive days at 8, 16, 24, 32, and 36 weeks of pregnancy and at three to six months after delivery, under the same conditions, with insulin, diet, and exercise identical

on both days, blood glucose was determined on fasting, one hour after breakfast, two hours after breakfast, and two hours after lunch. The differences at each of these four time points on two consecutive days were totaled and divided by four. This index is similar to MDD suggested by Molnar et al.,[3] though probably less sensitive since it's based on four points only, and not on continuous blood glucose monitoring. (2) The within-day glycemic excursions were calculated as the mean of the three absolute differences of blood glucose determined on the same day between the following points: fasting and one hour after breakfast, one hour and two hours after breakfast, two hours after breakfast, and two hours after lunch. This parameter reflects not only the essential brittleness but improper therapy (for instance, too low or too high morning dose of regular insulin, incorrect timing or composition of meals, etc.) and the Somogyi effect as well. Therefore, it cannot be used per se as an index of brittleness without reservations, but it can be useful in a longitudinal study of the carefully selected cases, with each patient serving as her own control.

In addition, we calculated the mean diurnal glycemia (the mean of the four points noted above).

### *The Patients*

Among 75 pregnant severe diabetics, eight had MDD values over 100 mg./100 ml. before pregnancy. The patients were 21-33 years of age (M.±S.E.M. 26±1.2 years), with their diabetes known for 8-18 years (M.±S.E.M. 13±1.2 years). All were of normal weight, and none suffered from nephropathy; four had minimal background retinopathy. Gestational age was 242-258 days since the last menstrual period (M.±S.E.M. 254±1.8 days). All the infants were born in good condition, with weight of 2,300-3,850 gm. (M.±S.E.M. 2,948±231 gm.); only two of them had weight above the 95th percentile. The patients visited the clinic, on the average, 46 times during their pregnancies. There were no cases of ketoacidosis and only three cases of transient 1+ ketonuria. The total weight gain was 9-14 kg.

Before pregnancy the patients underwent another study that showed that in them multiple insulin injections had no advantage over a single daily injection. At the beginning of pregnancy such an attempt was repeated. Two patients were found to be better controlled by two daily injections of NPH insulin. The other six were equally well (or, rather, equally badly) controlled by one or two injections of NPH (alone or together with regular insulin) or Lente insulin; they were treated by a single daily injection of either of these long-acting preparations. All the patients tested their urines regularly for glucose and ketones, and two of them tested their blood glucose daily (with Dextrostix). All the patients received three meals and three snacks a day.

The brittle diabetics were compared with 29 more stable diabetics of similar age (M.±S.E.M. 28±1.0 years), duration of diabetes (M.±S.E.M. 10±1.0 years), and gestational age (M.±S.E.M. 256±2.1 days) who gave birth to infants of similar weight (M.±S.E.M. 3,220±128 gm.). These patients were chosen on the basis of their MDD values' being normally distributed around the modal; their MDD values were 15-85 mg./100ml. (M.±S.E.M. 49±3 mg./100ml.). In fact, they simply represented the more typical and usual group of relatively stable diabetics, and the fact that they differed from the brittle diabetics in their MDD before and at the beginning of the pregnancy is clear from the definition. An additional control group consisted of 10 age-matched pregnant women with proved normal glucose tolerance.

Statistical evaluation was done by the Student's *t*-test and by paired *t*-test.[4]

## RESULTS

The main results are presented in the table and the figure. Though at any one point of time the insulin requirement of the brittle diabetics was not different from that of the stable patients, their over-all requirement was significantly lower (paired *t*-test: $t = 14.3$; $P<0.001$). The within-day variability of the stable diabetics was higher than in the nondiabetics at the beginning of the pregnancy, but the difference became nonsignificant after 24 weeks. The within-day variability of the brittle diabetics was at all times higher than in the other groups. The between-day variability (MDD) was significantly higher in both groups of diabetics than in the nondiabetics. In the brittle diabetics MDD was much higher than in the stable ones in the first half of their pregnancies, but the difference disappeared later, only to reappear after delivery. These changes took place in all brittle diabetics and were highly significant ($P<0.001$). All these changes resulted, naturally, in a lower mean daily glycemic level.

The aim of insulin therapy during pregnancy is to lower blood glucose as much as possible without causing hypoglycemia. The frequency of hypoglycemic episodes is undoubtedly the limiting factor in determining the upper limit of dose.[5] Mild hypoglycemia

was observed in stable diabetics, on the average, two times a month both before and during pregnancy; in brittle diabetics the corresponding frequency was six and five. Severe hypoglycemic reactions with loss of consciousness occurred during pregnancy only in the brittle diabetics (nine episodes in four patients, all of them in the first two trimesters).

## DISCUSSION

Our data show that with the progression of pregnancy both within-day and between-day glycemic variations substantially decreased; after 24 weeks the mean daily differences (the measure of brittleness) and the mean diurnal blood glucose levels in brittle and stable diabetics were similar. It should be noted that the clinical features show continuous variations of stability, so that some patients are extremely stable, others extremely brittle, and the great majority in between.[15] Among the patients under our observation, when the Somogyi effect was eliminated,[2] it turned out that the MDD (an index of brittleness) was normally, unimodally distributed in the group of 100 severe diabetics (unpublished observations). Therefore, the designation "brittle" is arbitrary and depends on the views of the investigators on the subject. We set the limit of severe brittleness at an MDD level of 100 mg./100 ml. Our control group was chosen to represent the modal MDD of severe diabetics (49±3 mg./100 ml.) and differed from the group of brittle diabetics by definition. The aim of its inclusion was merely to follow it longitudinally and to find out whether the difference between stable and brittle diabetics held true throughout the pregnancy; it turned out that it did not.

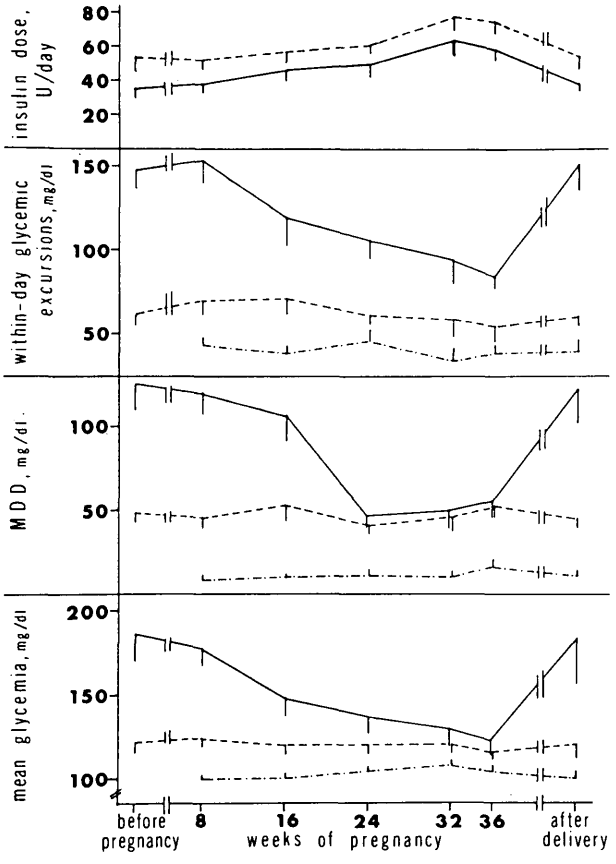


FIG. 1. Changes in insulin dose, within-day glycemic excursions, mean between-day variability of glycemia (MDD), and mean diurnal glycemia in the course of pregnancy in eight brittle diabetic (————), 29 stable diabetic (--------), and 10 nondiabetic (-.-.-.-) subjects (M. ± S.E.M.).

The within-day glycemic excursions are a useful measure of diabetic instability. Our data are somewhat lower for stable and much higher for brittle pregnant diabetics than were found by Persson and Lunell;[6] the discrepancy can probably be explained by the fact that the latter authors did not distinguish between the two subgroups. In general, the diurnal plasma glucose range in insulin-dependent pregnant diabetics was found to be almost three times higher than in nondiabetics.[7]

The difference between the fasting blood glucose values on successive days correlates well with the MDDs of continuously monitored paired blood-glucose values but cannot distinguish between stable and brittle diabetics.[8] When we used four points of reference for the calculation of MDD, the index clearly distinguished between the groups.

Since the brittleness is a quantitative rather than a qualitative phenomenon, it is obvious that the brittle patients chosen precisely because their MDD was on the right side of the distribution curve were different from those clustered around the modal value. What became evident by the second half of pregnancy was a kind of reduction to the mean, so that the data of brittle diabetics approached those of the main group of more stable patients. Still more important is the longitudinal observation on brittle diabetics themselves, which showed substantial decrease in MDD in all around the middle of their pregnancies.

The mechanism of brittleness in diabetes is unknown. The most brittle patients show the minimal increase in endogenous insulin secretion during glucose and arginine stimulation and negligible glucagon reaction to hypoglycemia;[15] we know of no comparable longitudinal studies in brittle pregnant diabetics.

TABLE 1

Insulin requirement, within-day glycemic excursions, mean of daily differences of blood glucose, and mean daily glycemia in eight brittle pregnant diabetics, 29 stable pregnant diabetics, and 10 healthy pregnant women (M. ± S.E.M.) (NS—not significant)

| | Before pregnancy | Weeks of pregnancy 8 | 16 | 24 | 32 | 36 | 3-6 months after delivery |
|---|---|---|---|---|---|---|---|
| Insulin requirement, U./day: | | | | | | | |
| Stable diabetics | 53±7.6 | 52±6.8 | 57±7.3 | 62±6.2 | 78±7.3 | 75±6.8 | 55±8.3 |
| | >N.S. | <N.S. | <N.S. | >N.S. | >N.S. | >N.S. | >N.S. |
| Brittle diabetics | 35±5.3 | 38±5.3 | 47±6.2 | 50±7.3 | 64±8.0 | 60±6.3 | 39±5.2 |
| Within-day glycemic excursions, mg./100 ml.: | | | | | | | |
| Nondiabetics | | 43±5 | 38±6 | 46±7 | 34±8 | 38±6 | 40±7 |
| | | >P<0.01 | >P<0.01 | >N.S. | >N.S. | >N.S. | >P<0.05 |
| Stable diabetics | 62±7 | 70±8 | 72±9 | 62±6 | 58±10 | 55±9 | 60±5 |
| | >P<0.001 | >P<0.001 | >P<0.02 | >P<0.005 | >P<0.05 | >P<0.05 | <P<0.001 |
| Brittle diabetics | 147±10 | 153±12 | 120±17 | 106±11 | 93±12 | 85±9 | 150±13 |
| Mean of daily differences of blood glucose, mg./100 ml.: | | | | | | | |
| Nondiabetics | | 8±3 | 9±2 | 12±1 | 10±3 | 16±3 | 10±2 |
| | | >P<0.001 | >P<0.001 | >P<0.001 | >P<0.001 | >P<0.001 | >P<0.001 |
| Stable diabetics | 49±3 | 42±6 | 51±7 | 39±4 | 44±5 | 53±5 | 40±3 |
| | >P<0.001 | >P<0.001 | >P<0.005 | >N.S. | >N.S. | >N.S. | >P<0.001 |
| Brittle diabetics | 127±11 | 120±12 | 108±14 | 46±7 | 48±9 | 55±8 | 128±15 |
| Mean daily glycemia, mg./100 ml.: | | | | | | | |
| Nondiabetics | | 98±4 | 100±5 | 104±4 | 108±5 | 105±6 | 97±6 |
| | | >P<0.005 | >P<0.025 | >P<0.05 | >N.S. | >N.S. | >P<0.025 |
| Stable diabetics | 121±8 | 126±7 | 119±7 | 120±8 | 122±8 | 116±6 | 119±9 |
| | >P<0.005 | >P<0.005 | >N.S. | >N.S. | >N.S. | >N.S. | >P<0.01 |
| Brittle diabetics | 184±18 | 177±13 | 148±16 | 139±17 | 130±18 | 125±16 | 182±25 |

Probably a study of C-peptide reactivity will throw light on the problem. In pregnant diabetics, glucagon, cortisol, and chorionic somatomammotropin were found to be normal,[6,9,10] but in those studies no distinction between brittle and more stable patients was made.

Since it is highly probable that the most brittle diabetics have virtually no endogenous insulin and glucagon secretion, the decrease in brittleness in the second half of pregnancy probably cannot be in any way explained by the changes in pancreatic function, and the explanation should be sought in extrapancreatic mechanisms. The most important factor is the placenta, and its secretions may influence blood glucose, but we have no information concerning the influence of placental hormones on the stability of the diabetes (as distinct from insulin requirement and its changes in the course of pregnancy).

Another possible factor could be insulin antibodies. In insulin-treated diabetics, antibodies against insulin have been held to smooth and prolong the effects of exogenous insulin. It was found that in brittle diabetes the antibodies were absent or only of low insulin-buffering power.[11] This was suggested as a cause of greater instability of diabetes towards the end of pregnancy,[12] but no clinical data were presented to substantiate the claim. Insulin antibodies in pregnancy were found to decrease in titer[13] or not to change at all.[14] In our nonpregnant diabetics we found no correlation between the insulin-binding capacity and brittleness (unpublished observations). Our data for brittle pregnant diabetics are limited to two cases only; in them no difference was found in the insulin-binding capacity between term and three months postpartum. It seems that the changes in insulin antibodies can hardly explain the decrease in brittleness in the second half of pregnancy.

Brittle diabetes is notoriously difficult to control. The proneness to hypoglycemia prevents increasing the insulin dose. When the brittleness in the course of pregnancy decreased, it permitted the insulin dose to be increased without undue danger of severe hypoglycemia. The over-all result was a decrease in mean diurnal glycemic level. Thus, it seems that the unpredictable form of severe diabetes becomes much more amenable to control in the second half of pregnancy, with resulting beneficial effects to the fetus.

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