# DIABETES MELLITUS AND PREGNANCY

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FOR many years following the appearance of Duncan's paper in 1882, diabetes was regarded as one of the most serious complications of pregnancy. In 1909, Williams stated that its gravity had been overestimated, yet at present there exists a great divergence of opinion concerning its importance as a complication of pregnancy and one meets with conflicting statements as to its significance. There are, however, certain points about which there is a general consensus of opinion; namely, that only a small number of diabetic women, perhaps not over 5 per cent, become pregnant; there is a high incidence of abortion or premature labor; when labor progresses to term the children are usually above the average in size; hydramnios seems to be a frequent complication; and the presence of sugar can usually be demonstrated in the amniotic fluid.

Vignis and Barbaro believe that diabetes developing during pregnancy is not so grave a complication as when it existed prior to conception, and in the latter case that the prognosis is especially unfavorable. Weiner also regards it as a very grave complication, and he states that the strain of pregnancy is severe on the pancreas. He holds that it cannot be warded off by insulin, and that women suffering from severe or moderately severe diabetes should not become pregnant, and when they do, that early interruption is indicated. Umber and others have also reported disastrous results in pregnancy complicated with diabetes.

On the other hand, certain authors do not agree with this contention. The work of both Morriss, and Rowley shows that at birth the maternal blood sugar is higher than the fetal. The latter author, as well as Brigham, believes that insulin will reduce to practically nothing the grave dangers of pregnancy complicated by diabetes. Lubin states that mild diabetes is often not aggravated by pregnancy, while Peters reports a case of diabetes which was carried to near term with insulin without serious results. As the entire literature upon the subject has recently been summarized by Lambie, the reader is referred to his article for further literary details.

It is because of this difference of opinion, that we have been interested in studying the metabolism of several diabetic patients during the course of repeated pregnancies. An attempt has been made to have the patient in the hospital for a period of two weeks at intervals during her pregnancy, in order that one may gain fairly accurate information as to the diabetic condition. She is studied not only during the pregnancy, but also for as long a period as possible after delivery. It should be remembered that our conclusions are not based on the study of a single pregnancy, but upon the data obtained during the course of four or five consecutive pregnancies in the same individual.

TABLE I. METABOLISM CHART OF FOURTH PREGNANCY OF PATIENT 1

*(Similar Charts Were Employed in All of Our Studies)*

| DATE 1926 | URINE | | | | | | BLOOD | | | DIET ORDERED | | | DIET RECEIVED | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | C.C. | SUGAR % | SUGAR GM. | ACETONE | DIACETIC | TOTAL N. | SUGAR | N. P. N. | $CO_2$ | P. | F. | C. | P. | F. | C. |
| Jan. 12 | 1320 | .71 | 9.4 | 0 | 0 | 7.4 | .147 | 31.5 | 48.0 | 50 | 160 | 70 | 50.0 | 161.0 | 69.0 |
| 13 | 295 | .65 | 2.0 | 0 | 0 | 2.6 | | | | 40 | 140 | 58 | 41.0 | 140.0 | 55.0 |
| 14 | 920 | .78 | 5.8 | 0 | 0 | 8.7 | | | | 40 | 140 | 58 | 40.8 | 140.0 | 59.0 |
| 15 | 780 | .59 | 4.6 | 0 | 0 | 11.0 | .145 | 33.0 | 44.0 | 40 | 140 | 58 | 32.0 | 98.0 | 38.0 |
| 16 | 840 | .72 | 5.85 | 0 | 0 | 4.3 | | | | 40 | 140 | 58 | 39.0 | 127.0 | 53.0 |
| Feb. 1 | 1280 | .195 | 2.49 | 0 | 0 | 8.7 | | | | 40 | 140 | 58 | 36.8 | 130.0 | 58.6 |
| 2 | 1265 | .247 | 3.12 | 0 | 0 | 8.9 | | | | 40 | 140 | 58 | 30.0 | 103.0 | 49.0 |
| 3 | 1080 | .21 | 2.26 | 0 | 0 | 9.2 | | | | 40 | 140 | 58 | 36.0 | 124.0 | 56.0 |
| 4 | 1020 | .19 | 1.93 | 0 | 0 | 6.7 | .154 | 30.0 | 50.5 | 40 | 140 | 58 | 41.0 | 140.0 | 58.0 |
| 5 | 780 | .39 | 3.04 | 0 | 0 | 8.2 | | | | 40 | 140 | 58 | 34.0 | 117.0 | 53.0 |

TABLE I.—CONT'D

| DATE 1926 | DIET METABOLIZED | | | | | | CAL. REQUIRED | CAL. RECEIVED | WT. | HT. | INSULIN |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | P. | F. | C. | AV. GL. | AV. FA. | FA/G | | | | | |
| Jan. 12 | 46.25 | 156.0 | 59.6 | 102.0 | 160.7 | 1.6 | 1701 | 1985 | 88.6 K | 164.7 cm. | 0 |
| 13 | 16.25 | 151.9 | 52.9 | 77.5 | 143.9 | 1.9 | 1701 | 1697 | 85 K | | 0 |
| 14 | 57.37 | 136.7 | 53.2 | 98.4 | 146.9 | 1.5 | 1701 | 1712 | | | 0 |
| 15 | 68.75 | 83.8 | 33.4 | 81.6 | 105.6 | 1.3 | 1701 | 1198 | | | 0 |
| 16 | 26.88 | 134.9 | 47.1 | 76.2 | 133.2 | 1.7 | 1701 | 1558 | | | 0 |
| Feb. 1 | 54.7 | 123.2 | 56.1 | 101.1 | 134.9 | 1.3 | 1701 | 1600 | 85.5 K | | 45 |
| 2 | 55.6 | 93.1 | 45.9 | 87.5 | 108.2 | 1.3 | 1701 | 1281 | | | 45 |
| 3 | 57.7 | 126.2 | 53.7 | 98.8 | 139.0 | 1.4 | 1701 | 1530 | | | 45 |
| 4 | 41.9 | 140.5 | 56.1 | 94.4 | 144.9 | 1.5 | 1701 | 1708 | | | 45 |
| 5 | 51.1 | 110.8 | 50.0 | 90.7 | 122.2 | 1.4 | 1701 | 1445 | | | 45 |

We have studied in detail three diabetic women,—two of whom presented four consecutive pregnancies, and one five consecutive pregnancies.

During all of our studies, the patient was in bed and upon a carefully regulated diabetic diet. Daily determinations were made of the amount of sugar, acetone, diacetic acid and total nitrogen in the urine, while the blood was analyzed at frequent intervals for non-protein nitrogen, sugar, and $CO_2$ combining power. The amount of food taken by the patient was carefully recorded and a complete metabolism chart kept. As it would require too much space to re-

TABLE II. (Case No. 1.—Patient H. M., Unit 1948, Born 1883, Colored)

| PREGNANCY | DATE | DURATION | URINE SUGAR | BLOOD SUGAR | F.A./G. | REMARKS |
|---|---|---|---|---|---|---|
| I | 1916 | Term | ---- | ---- | --- | Normal delivery. Child living. |
| II | 11/26/17 | Term | 0 | ---- | --- | Suffered from preeclampsia. Normal delivery. Child living. |
| III | 6/ 8/23 | 4½ mo. | 12.8 gm. | 0.194 | 1.6 | In July, 1919, it was discovered that the patient had diabetes, with 33 gm. of sugar in the urine, on admission to the Medical Clinic. She received treatment with insulin for 2 mo. and was discharged with no sugar in urine and with a normal blood sugar. |
| | 6/26/23 | 5 mo. | 2.3 gm. | 0.167 | 1.5 | |
| | 7/10/23 | 6 mo. | 22.5 gm. | ---- | --- | |
| | 7/12/23 | 6 mo. | 0 | 0.182 | --- | |
| | 7/24/23 | +6 mo. | 20.7 gm. | ---- | --- | |
| | 7/27/23 | 6½ mo. | 0 | ---- | --- | Spontaneous premature delivery of stillborn child, premature separation of placenta. Patient was discharged 8/28/23 and was then lost track of until in the subsequent pregnancy in 1925, as shown below. |
| | 7/28/23 | 1 day p.p. | Faint trace | 0.207 | --- | |
| | 8/28/23 | 1 month p.p. | 14.4 gm. | ---- | --- | |
| IV | 1/12/26 | 3½ mo. | 9.4 gm. | 0.147 | 1.6 | No acetone or diacetic acid. |
| | 2/ 5/26 | 4½ mo. | 3.0 gm. | 0.154 | 1.4 | Discharged after getting 45 units insulin a day for past 2 weeks. |
| | 3/10/26 | 5½ mo. | 1.0 gm. | 0.153 | 1.6 | Receiving 40 units insulin a day. |
| | 5/ 1/26 | +7 mo. | 1.2 gm. | 0.091 | 1.6 | Receiving 38 units insulin a day. |
| | 5/19/26 | 8 mo. | 1.9 gm. | 0.095 | 1.4 | Receiving 38 units insulin a day. |
| | 6/ 5/26 | 9 mo. | 0 | 0.118 | 1.1 | *No* insulin since 6/3/26. |
| | 6/ 8/26 | 9 mo. | 0 | 0.149 | 1.1 | Labor induced because of vomiting. Child weighed 2750 gm., living. |
| | 6/15/26 | 7 days p.p. | 0 | 0.158 | 1.9 | Vomiting stopped. Patient in good condition. |
| | 6/18/26 | 10 days p.p. | No dextrose. Positive for lactose. | 0.182 | 1.9 | Discharged without insulin. |

produce the complete charts of all the patients, we are giving the figures for two five-day periods (Table I) during one of the admissions of H. M., in the hope that it will give an idea as to how our determinations were made. The data from all the charts have been condensed into tables and are shown in Tables II, III and IV. Each of these three tables records the essential data observed in the consecutive pregnancies of the same woman. The data as to parity and the duration of pregnancy are given in order that one may follow the progress of each pregnancy. The amount of sugar in the urine, in grams wherever possible, otherwise in percentage, as well as the blood sugar in percentage are then given. The column "FA/G" represents the ratio of fatty acids to glucose as metabolized by the patient, and, of course, is of the greatest value in evaluating the

TABLE III. (Case No. 2.—Patient J. S., Unit 2840, Born 1887, White)

| PREGNANCY | DATE | DURATION | URINE SUGAR | BLOOD SUEAR | F.A./G. | REMARKS |
|---|---|---|---|---|---|---|
| I | 9/ 7/15 | Term | 0 | | | Normal delivery. Child living. |
| II | 1917 | Term | 0 | | | Normal delivery following a mild toxemia of pregnancy. Child living. |
| | 3/30/20 | Not pregnant | 0.3% | 0.194 | | Glycosuria first noted 1/1/20. Acetone and diacetic positive. Treated in Medical Department. |
| III | 5/ 4/20 | Not pregnant | 16 gm. | 0.217 | | She reports to Metabolism Clinic. |
| | 9/29/20 | 3 mo. | 5 gm. | | | During this pregnancy she attended the Dispensary every 2 weeks. Her urine remained sugar and acetone free throughout latter part of the pregnancy. |
| | 10/23/20 | 4 mo. | 0 | 0.084 | | |
| | 11/12/20 | 5 mo. | 0 | 0.090 | | |
| | 3/ 9/21 | Term | 0 | | | Normal delivery. Child living, weight 3930 gm. |
| | 3/21/21 | 12 days p.p. | 0 | | | Discharged in good condition. |
| IV | 6/ 5/23 | Not pregnant | 0.1% | | | She has been visiting the Metabolism Clinic regularly. Diet: P. 60; F. 115; C. 50. |
| | 5/13/24 | 1 mo. | 6 gm. | | | No acetone. Diet: P. 60; F. 150; C. 45. |
| | 8/12/25 | 4 mo. | 4.6 gm. | 0.174 | | Acetone +; Diacetic 0. |
| | 9/ 7/24 | 5 mo. | 0 | 0.187 | 1.5 | Diet: Glycerine + P. 70; F. 155; C. 50. |
| | 11/11/24 | 7 mo. | 0 | 0.122 | 1.5 | Acetone +; Diacetic +; Diet as above. |
| | 1/ 6/25 | + 8½ mo. | 0 | | | Acetone and Diacetic negative. Diet same. |
| | 1/20/25 | – Term | 0 | 0.121 | | Normal delivery. Child living. Weight 4670 gm. Acetone 0. |
| | 1/23/25 | 3 days p.p. | 0 | 0.118 | | Acetone-free. |
| | 3/ 3/25 | 1½ mo. p.p | 0 | | | Acetone-free. |
| | 7/14/25 | 6 mo. p.p | 7.5 gm. | | | Patient has been making regular visits to the Metabolism Clinic and is adhering fairly well to prescribed diet. |
| | 7/27/26 | 1½ yr. p.p. | 6.8 gm. | | | |

patient's condition. Under "Remarks" we give a brief and concise outline of the clinical condition, as well as such further information as may aid one in following the progress of the pregnancy and the diabetes.

CASE 1.—The patient, H. M. (Table II), had severe diabetes. Her third pregnancy terminated in premature delivery at 6½ months, and she was discharged one month later with a high blood sugar level and sugar in the urine. Her condition during this pregnancy was decidedly unfavorable. The following (fourth) pregnancy was studied in detail and the carbohydrate metabolism was carefully determined at regular and frequent intervals. During this pregnancy, the findings, as summed up in the latter part of Table II, clearly indicate that the diabetic condition started to improve during the fourth or fifth month of pregnancy, and the improvement continued up to term. The patient was discharged 10 days after delivery without dextrose in the urine, but with an elevated blood sugar.

CASE 2.—The patient, J. S., was studied during four consecutive pregnancies, and probably developed diabetes after second pregnancy. The urine and blood determinations, as shown in Table III, indicate that in both the third and fourth pregnancies, the diabetic condition improved at about the fourth or fifth month and that the improvement continued up to term. At the time of both labors, the urine was sugar-free and the blood sugar at a normal level. This relatively satisfactory condition continued for over two months postpartum, but when the patient was seen six months after delivery, the diabetes had returned. It will also be noted that although the urine was positive for both acetone and diacetic acid during the early months of pregnancy, both substances disappeared from the urine as term was approached.

CASE 3.—The patient, M. M., was observed during five consecutive pregnancies. In 1916, shortly after the third pregnancy, it was discovered that she had diabetes mellitus, with a blood sugar of 0.237 per cent and 4 per cent of sugar in the urine. She received treatment in the Medical Clinic and improved rapidly. We were unable to follow her during the following or fourth pregnancy, but carried out repeated metabolism studies during the last, or fifth pregnancy. Our findings are summarized in Table IV. From their study it will be seen that when the patient was first observed at the seventh month of her fifth pregnancy, she had a high blood sugar and almost 4 grams of sugar in the urine. From that time on, her condition continued to improve so that a few days before delivery the blood sugar was within normal limits and the urine was sugar-free. It must, however, be pointed out that we had increased the amount of insulin from 10 units to 30 units a day; but as shown in the postpartum studies, the patient remained sugar-free and with a normal blood sugar for 8 months, although at that time she was receiving no insulin.

Before entering into a general discussion of our results, we wish to report a study of a mild case of diabetes mellitus. Several workers have stressed the necessity of careful diagnosis of a glycosuria developing during pregnancy, and of differentiating lactosuria, alimentary glycosuria, or renal glycosuria due to a kidney hyperpermeable to glucose, from true diabetes mellitus. We believe that, in this last case, the presence of a slightly elevated blood sugar and of acetone bodies in the urine three months postpartum indicate that we had to deal with a true, though mild diabetes.

TABLE IV. (Case No. 3.—Patient M. M., Unit 2103, Born 1888, White)

| PREGNANCY | DATE | DURATION | URINE SUGAR | BLOOD SUGAR | F.A./G. | REMARKS |
|---|---|---|---|---|---|---|
| I | 1906 | Term | 0 | | | Normal delivery. Child living. |
| II | 1914 | Term | | | | Normal delivery. Child living. Considerable edema and headache. |
| III | 1916 | Term | ? | | | Normal delivery. Child living. Two months later patient admitted to medical clinic with diagnosis of diabetes; blood sugar 0.237 and 4% sugar in urine, with acetone and diacetic present. Treated and discharged with urine sugar free and blood sugar 0.109. |
| IV | 1922 | Term | | | | Normal delivery. Child stillborn. In 1918 patient was in medical clinic and urine was sugar-free. |
| | 2/18/25 | 7 mo. | 3.72 gm. | 0.182 | 1.9 | She had been referred to metabolism clinic 2/10/25, when 23 gm. sugar were found in 24 hour urine specimen. Receiving 10 units insulin a day. |
| V | 2/25/25 | 7¼ mo. | 1.98 gm. | 0.121 | 1.6 | Receiving 10 units insulin a day. |
| | 3/ 3/25 | 7½ mo. | Faint trace | 0.124 | 1.7 | Receiving 20 units insulin a day. |
| | 4/19/25 | +9 mo. | 0 | 0.118 | 1.6 | Receiving 30 units insulin a day. |
| | 4/21/25 | In labor | 0 | | 1.6 | Labor induced (bag). Child living. Weight 3090 gm. Receiving 30 units insulin a day. |
| | 7/28/25 | 3 mo. p. p. | 0 | 0.116 | | Receiving 24 units insulin a day. |
| | 1/21/26 | 9 mo. p. p. | 0 | 0.093 | 1.1 | Receiving *no* insulin. |

TABLE V. (Case No. 4.—Patient M. J., Unit 4123, Born 1899, White)

| PREGNANCY | DATE | DURATION | URINE SUGAR | BLOOD SUGAR | F.A./G. | REMARKS |
|---|---|---|---|---|---|---|
| I | 4/21/26 | 3 mo. | 8.8 gm | 0.143 | 1.1 | Diet: P. 47; F. 67; C. 108; |
| | 4/28/26 | +3 mo. | 1.9 gm | 0.133 | 1.2 | acetone and diacetic negative throughout this month. |
| | 6/28/26 | +5 mo. | 0 | 0.143 | | Acetone and diacetic negative. |
| | 10/12/26 | Term | 0 | | | Low forceps delivery. Child normal, 3398 gm. Acetone and diacetic negative. |
| | 10/15/26 | 3 days p. p. | 0 | 0.087 | 1.6 | No insulin throughout the pregnancy. |
| | 1/11/27 | 3 mo. p. p. | 0 | 0.130 | | Diacetic and acetone both positive. $CO_2$ 63.3 vol. per cent. |

CASE 4.—The patient, M. J., was first seen in the Prenatal Service on April 13, 1926, when she was about 3 months pregnant. She had been told by her private physician that she had sugar in the urine. We studied her throughout this pregnancy and the findings are summarized in Table V. She was kept on a diabetic diet throughout the pregnancy, as well as for three months following the delivery of a normal child at term. From the data reported, it will be seen that at about the fifth month of pregnancy the urine became sugar-free, although the blood sugar was slightly elevated. At term, the urine was still without sugar and the blood sugar was at a normal level. The postpartum studies showed that the urine re-

mained negative for sugar, although the blood-sugar level gradually rose and acetone and diacetic acid appeared in the urine. It is thus fairly evident that at about the fifth month of pregnancy the diabetic condition improved, that at term the patient was without signs or symptoms of diabetes, and that this condition persisted for some time into the puerperium.

## DISCUSSION

In 1911, Carlson and Drennan reported experiments relating to the control of pancreatic diabetes in pregnancy. They found that in eight to sixteen hours after pancreatectomy in normal dogs, glycosuria appears, reaching a high point within twenty-four to thirty-six hours post operationem. Identical results were also obtained in early pregnancy, but in dogs at or near term, no sugar appeared in the urine following operation. (But within fourteen hours following delivery by abdominal section, sugar reappeared in the urine.) Two years later Lafon suggested that the absence of glycosuria in depancreatized dogs at term was due to the passage of fetal hormones to the mother and that the fetuses were able to dispose of the excess of maternal blood sugar by oxidation or storage without any embarrassment to their own carbohydrate metabolism. In 1916, Falco endeavored to explain the results of Carlson and Drennan on the supposition that the surplus of maternal blood sugar is metabolized by placental ferments.

Dubreuil and Anderodias reported the case of a diabetic mother who gave birth at the eighth month to a 5000 gram child, whose pancreas showed huge masses of Island of Langerhans tissue. They thought that the continual passage of blood sugar from mother to fetus accounted for the size of the child, as well as for the increase in the amount of island tissue, which they believed developed for the protection of the child against hyperglycemia. Holzbach likewise reports a case of pregnancy associated with edema, hydramnios, ketonuria, glycosuria and a blood sugar of 0.120 per cent. Upon the death of the child in utero the blood sugar rose to 0.210 per cent and the sugar in the urine increased from 10 to 44 grams. At birth the child was stillborn and weighed 4200 grams.

It is essential that the mother be under observation for a period of two or more years after the delivery before we can draw any definite conclusions as to the effect of pregnancy on the course of diabetes mellitus. Springer quotes Colorni as stating that 46 per cent of diabetic mothers die during the first two years postpartum, but the data here presented show that this has not been our experience. From a consideration of the experimental results and of our clinical evidence it appears that pregnancy, particularly during its latter half, may be associated with a change in the maternal carbohydrate metabolism, with the result that in the diabetic, the tendency towards hyperglycemia may be decreased or even disappear during the latter half

of pregnancy. How this is brought about we do not know, but the factors responsible for this may be a pancreatic hormone coming from the fetus, a greater demand by the fetus for maternal carbohydrates, or some other as yet unknown mechanism. The work of one of us on the respiratory exchange of the fetus suggests that the fetus uses, at least when near term, carbohydrates for its source of energy, and we have pointed out that there is an unusual demand on the maternal sugar by the fetus.

## SUMMARY

Metabolism studies on three patients who suffered from diabetes during repeated and consecutive pregnancies, as well as on a mild diabetic patient in a single pregnancy, were conducted at regular intervals during the state of gravidity, as well as during the puerperium and later. In order to evaluate the severity of the diabetic complication, a complete diabetic chart, as used in this hospital and as shown in Table I, was carefully kept in each case. The main items of these charts, viz., the urine sugar, the blood sugar and the fatty acid to glucose ration (F.A./G.) are summarized for each patient in the several charts, which also contain the information as to the presence or absence of acetone and diacetic acid in the urine, and as to the patient's diet and treatment. The amount of sugar in the urine, the presence or absence of acetone and diacetic acid, the blood-sugar level and the F.A./G. ratio give us a fairly good index of the diabetic condition. Reference has been made to some of the important clinical and experimental findings reported by other workers.

## CONCLUSIONS

1. The diabetic woman may undergo a change for the better during the second half of pregnancy.

2. This improvement may be due to the action of fetal pancreatic hormone, to an excessive utilization of maternal carbohydrate by the fetus, as well as to some as yet unknown change in the maternal carbohydrate metabolism which takes place in the latter stages of gravidity.

3. Under careful hospital supervision as to diet, with frequent urine and blood analyses, and with insulin treatment if necessary, the diabetic patient may often go to term and be successfully delivered of a living child, without aggravation of the diabetic condition or indeed with a temporary disappearance of all symptoms during a part of the period of lactation. Of course, it would be unwise to anticipate such an outcome in extremely advanced cases of diabetes.

4. In patients with diabetes mellitus the first half of pregnancy appears to be the precarious period for the fetus, and without any benefit to the mother.

5. The excessive size of children born of diabetic mothers is probably due to the increased supply of maternal blood sugar, as the fetus undoubtedly makes a heavy demand on the maternal carbohydrates not only for its sugar requirements but also in order to build its fat and to supply its own energy.

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