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INTERACTIONS OF PREGNANCY AND DIABETES*

FRED W. WHITEHOUSE, M.D.**

The subject under discussion this morning is interaction of pregnancy and diabetes. Diabetes is a serious disease but with effective control is consistent with a long and useful life. When the diabetic woman is pregnant, additional problems occur. The prospective mother faces a 10-15% chance of loss of the baby by stillbirth or neonatal death compared to the non-diabetic mother whose baby has a 97% chance of survival. We will now discuss some current ideas about diabetes and pregnancy.

Dr. Miguel Solorio Riestra (Division of Metabolism): Mrs. A. C. is a 25-year-old colored female who was admitted to Henry Ford Hospital in November, 1966, for control of recently discovered diabetes mellitus. She is in the second trimester of her third pregnancy; her last menstrual period was in July, 1966. In 1962, Mrs. C. delivered a living infant who weighed 3600 Gm. Her second pregnancy, in 1964, ended in spontaneous abortion at 22 weeks. She has gained 5 pounds during this pregnancy. Her mother has diabetes mellitus.

On October 24, 1966, during a routine examination by her obstetrician, Dr. Melvern Ayres, she was found to have one-plus glycosuria, and a 2-hour post-cibal blood sugar was 250 mg. per 100 ml. Although asymptomatic at that time, she was given a 1500-Calorie diabetic diet. Two weeks later, because of persistent glycosuria, Mrs. C. was hospitalized for control of her diabetes. Her weight on admission was 161 pounds, height 67 inches, vital signs were normal, and the entire physical examination was negative except for uterine enlargement corresponding to a pregnancy of 4 months. During hospitalization the 1500-Calorie diet was continued and lente insulin, 16 units daily, was added. The patient became aglycosuric. On the eighth hospital day her fasting blood sugar was 110 mg. per 100 ml.

Dr. Fred W. Whitehouse (Division of Metabolism): Mrs. C. is unable to be with us this morning, but if she were here, she would tell us that she had been told of glycosuria during her first pregnancy. No blood sugars were obtained, and there were no examinations following delivery.

*Abridged transcript of a Tuesday Morning Medical Conference presented 6 December, 1966, in the Buerki Auditorium.

**Assisted by resident and senior staff colleagues from the Departments of Medicine, Obstetrics, and Pediatrics.

Dr. Zadvinskis, you saw Mrs. C. in your office after referral from her obstetrician. You confirmed the diagnosis of diabetes and placed her on a diet; 2 weeks later you decided that the diet was inadequate and advised her to enter the hospital for regulation with insulin. Why didn't you use one of the oral hypoglycemic agents?

Dr. Zadvinskis (Division of Metabolism): I did not advise an oral hypoglycemic agent for two reasons, the child and the mother.

The effects of oral hypoglycemic agents on the fetus still are not fully known. There have been scattered reports suggesting teratogenic effects of the oral hypoglycemic agents with an increase in perinatal mortality. In most pregnant women we are dealing with young diabetics who usually fail to respond to the oral agents. Carbohydrate tolerance often worsens even to the point of ketosis as pregnancy progresses. If this is true, the use of an oral hypoglycemic agent could be dangerous. Ketosis is a great killer of unborn babies. Insulin is physiologic, is always effective when used correctly, and will secure the best control of the diabetes.

Dr. Whitehouse: An important objection to the oral hypoglycemic agents during pregnancy is a restrictiveness of therapy consequent to their use which doesn't exist with insulin. One must keep in mind that a sulfonyleurea releases only a small amount of insulin. In our patient we wish to avoid any restrictiveness in therapy. Broad changes in insulin requirement may occur in the pregnant diabetic. It may not prove necessary, but the physician needs plenty of latitude. Therefore, insulin therapy is in order in patients with diabetes complicating pregnancy when there is inability to maintain good control of the diabetes by diet alone. We also know that there are unanswered questions regarding the teratogenicity of many drugs, and I would suggest that all diabetic women in the child-bearing age are candidates for insulin rather than for an oral agent. If an oral agent is used in young women, one must recall that by the time a diagnosis of pregnancy is made the teratogenicity of the oral agent will have affected the fetus. I admit, however, that no conclusive evidence exists to relate teratogenicity to any oral hypoglycemic drug.

Dr. Solorio, do you agree with Dr. Zadvinskis that, as pregnancy progresses, the insulin requirement will increase?

Dr. Solorio: Yes. Pregnancy affects carbohydrate metabolism adversely. Pregnant patients have decreased glucose tolerance possibly due to increased production of adrenal cortical hormones.

Dr. Whitehouse: Let's explore this point for a moment, and let me use the slide as a point of reference (Table I).

This is a simple-minded slide entitled "Diabetogenicity." It applies to the pregnant diabetic as well as to her non-diabetic peer. In the pregnant patient one might consider three aspects of diabetogenicity. There may be several hormonal mechanisms related to the diminution of glucose tolerance. In my view, the increase in estrogens and

PREGNANCY AND DIABETES

Table I. The "diabetogenicity" of pregnancy.

- A. Hormonal.
 - 1. Estrogen - progesterone.
 - 2. Placental lactogen ("G.H.—like").
 - 3. Corticoids.
- B. Enzymatic degradation by placenta.
- C. "Insulinogenic reserve."

progesterone plays a small role in the diabetogenicity of the pregnant state. We do know that in careful studies of patients on oral contraceptive agents, one is able to identify mild abnormalities in glucose tolerance.¹ These are minor changes when compared with the alterations in glucose tolerance associated with pregnancy.

A more interesting substance is one recently studied by Josimovich and co-workers.^{2,3} They have described a growth-hormone-like protein which is named human placental lactogen (HPL). Others⁴ refer to this substance as chorionic "growth-hormone-prolactin." HPL has many immunological characteristics of growth hormone, yet it is biochemically distinct. Concentration of HPL is much greater in retroplacental serum than in peripheral blood. This and other evidence suggests that HPL is produced by the placenta, probably by the trophoblast. HPL has actions similar to growth hormone; indeed, it may potentiate the action of growth hormone as well as manifest primary physiologic effects. There is growth-promoting activity in immature hypophysectomized animals. HPL may be essential for the development of the corpus luteum of pregnancy. Lipolysis is stimulated by HPL; this results in an increase in circulating free fatty acids (FFA). This elevation of FFA is one mechanism by which the peripheral effect of insulin may be blunted. Thus it seems reasonable to suggest that human placental lactogen is one of the substances which plays a major role in the diabetogenicity of pregnancy.

Dr. Solorio has indicated that corticoids may have an adverse effect on glucose tolerance, and in just a moment I am going to ask Dr. Mellinger to comment on this particular point. I wonder whether the circulating corticoids really are biologically significant in the diminution of carbohydrate tolerance in pregnancy. It's just possible they are biochemically measurable yet biologically inactive.

We must credit the enzymatic degradation of insulin by the placenta with a major role in the diabetogenicity of pregnancy. There are proteolytic enzymes in the placenta which inactivate insulin; though no insulin-glutathione transhydrogenase has been identified. Freinkel and Goodner have reviewed this subject recently.⁵

Then let us remember "insulinogenic reserve." This term refers to one's capacity to produce insulin under stress. Individuals lacking this "reserve" are probably genotypic diabetics. Our patient is an example. Glycosuria occurred during one pregnancy;

now overt diabetes exists. After delivery Mrs. C. may demonstrate improvement in her florid diabetes. With no placenta less stress will be placed on her "insulinogenic reserve."

Dr. Mellinger, will you comment now on this problem of circulating corticoids in pregnancy?

Dr. Raymond C. Mellinger (Division of Endocrinology): Plasma and urinary 17-hydroxycorticosteroids rise measurably with pregnancy. Plasma levels are elevated disproportionately, a fact which is explained by the increased binding capacity of the serum proteins. In response to estrogens, either administered exogenously or derived from endogenous sources in pregnancy, the plasma factor, transcortin, increases greatly. This globulin binds cortisol and increases the assayable plasma steroids. However, the bound steroid is not biologically active, and as Dr. Whitehouse has suggested, the free active steroid moiety is not increased by estrogens or by the pregnant state.

On the other hand, it has been claimed in the past that a woman with Addison's disease is improved by pregnancy. Certainly that remarkable endocrine organ, the placenta, is capable of producing steroid hormones. Although some of these are measurable as a corticosteroid fraction, it has been shown that the placenta does not secrete significant amounts of cortisol. It is my belief that the glucocorticoid-like steroid of the placenta is a 6-beta-hydroxy-steroid, which is not biologically active, as is cortisol. In fact, recent and more careful studies indicate that the pregnant patient with Addison's disease is not improved by the pregnancy, and the corticosteroid supplements cannot be curtailed during the gravid state.

In summary, urinary and plasma corticosteroids, as measured by conventional tests in pregnancy, are present in elevated titers. The biologic effect of these steroids, however, is of little or no significance to the carbohydrate metabolism as far as we now know.

Dr. Whitehouse: We have said that potentiation of the action of growth hormone by placental lactogen results in elevated circulating levels of free fatty acids (FFA). If the level of FFA is increased non-specifically in pregnant animals with the use of heparin, one is able to demonstrate increased deposition of fatty tissue in the offspring of these animals. Dr. Dew, will you comment briefly on the problem of the big baby, the fetal giants, in the patient with diabetes or in the woman who develops diabetes in later life.

Dr. Richard Dew (Division of Metabolism): A newborn with a birth weight in excess of 4000 grams is a frequent result of diabetes complicating pregnancy. This relationship also pertains to the woman who develops diabetes some years after the pregnancy. These observations are retrospective; what is needed is a long-term prospective study. This type of experimental design would permit accurate estimation of the frequency of fetal giantism as a stigma of genotypic diabetes. Little information

PREGNANCY AND DIABETES

is available now on the reasons for these fetal giants. One must also remember that many diabetics do not bear large babies. Perhaps senescent placental changes are important here.

Dr. Whitehouse: Desiccation experiments demonstrate an increase in total body fat in these fetuses as well as an increase in total body water. If Dr. Robert High would examine one of these babies immediately post-partum, he would probably feel that they demonstrate increases in fat and in water. Is that correct, Dr. High?

Dr. Robert High (Department of Pediatrics): Yes, it is.

Dr. Whitehouse: All credit for the diagnosis of diabetes in this patient goes to Dr. Melvern Ayers, her obstetrician. Why did you obtain a urine test for sugar on Mrs. C., Dr. Ayers?

Dr. Melvern A. Ayers (Department of Obstetrics): All obstetrical patients have a urine test for albumin and sugar at each office visit. This is mandatory for all obstetrical visits regardless of the reason for the visit.

Dr. Whitehouse: This is proper. It is also proper to follow the dictum that "glycosuria is diabetes until proved otherwise." This was done in our patient and her diabetes was identified in an early stage.

Dr. Ayers, would you comment on early timing of the delivery on gestational morbidity and on late intrauterine death of the fetus. These are problems we face in the pregnant diabetic.

Dr. Ayers: The obstetrician's biggest problem is when to deliver the baby. Prematurity has to be balanced against the hazard of late intrauterine death in determining when the patient should be delivered. The mechanics of delivery are primarily the choice of the obstetrician. If the presenting part and the cervix are unfavorable, Caesarean section will be performed without any attempt at vaginal delivery. This is a matter of obstetrical judgment. When to attempt delivery is the most pressing problem. A study of perinatal mortality reveals that between 35 and 36 weeks, we will lose approximately 19 per cent of these infants. At 37 weeks, this loss will decrease to about 11 per cent. If one waits until 38 to 39 weeks, the perinatal mortality climbs to 26 per cent. Therefore, 36 to 37 weeks seems to be the optimal time to deliver the baby. What are the qualifying factors here? Regardless of what the percentages show, if this woman had delivered previously a stillbirth at 37 weeks, I would advise delivery prior to the gestational date of the stillbirth as long as this date is 35 weeks or more.

Dr. Whitehouse: How can you be sure that your gestational age is correct?

Dr. Ayers: This is an age-old question. We are all aware of the clinical signs. An accurate calendar of menstrual periods and knowledge of the previous menstrual

history is helpful. Repeated pelvic examinations early in the pregnancy to ascertain accurately the growth of the uterus offers information. Is it compatible with two months, three months, four months? When does the mother first feel the baby? When does the obstetrician first hear the fetal heart tones? These points all help one arrive at the correct gestational date. Complicating polyhydramnios may make fetal palpation very difficult. Other studies include flat films of the abdomen, particularly the oblique view, looking for calcification in the distal femoral epiphysis and in the proximal tibial epiphysis. Recently there has been a great deal of interest in the use of measurements of urinary estriol levels as a guide to fetal maturity and fetal distress. Dr. Gerald Roy will discuss this aspect.

Dr. Gerald J. Roy (Department of Obstetrics): Dr. Ayers has asked me about the usefulness of urinary estriol determinations in helping us to decide when to deliver a patient. Estriol is secreted in greatly increased amounts during pregnancy. Both placental and fetal metabolism play a role in this increase. Measurement of the 24-hour urinary estriol excretion can now be done in many laboratories. Following this parameter, placental insufficiency is identified by a drop in the urinary excretion of estriol. In the pregnant diabetic approaching term, I don't believe the estriol level will be particularly useful in telling us when to deliver a patient except for a few circumstances. But, in these few circumstances I think it may be very helpful. These may include the milder diabetic, Class A and Class B (White), in whom we desire to delay delivery as long as possible. In this group of patients the fetus is most threatened by placental insufficiency. Here, serial determinations of urinary estriol may be valuable, especially if measured every second day. If one can identify a significant drop in the level of urinary estriol early, we should have time to deliver the baby before intrauterine death occurs.

Dr. Whitehouse: Drs. Robert Thompson and Walter Berberich of the Department of Obstetrics are working on this problem now and we hope to be able to apply their experience to our pregnant diabetics. We would like to be forewarned regarding intrauterine fetal death so that we can carry these women as close to term as possible in order to avoid the hazards of prematurity.

Dr. Solorio, what do you predict the insulin requirement of Mrs. C. will be in the post-partum state?

Dr. Solorio: After delivery there often is a precipitous fall in the daily insulin requirement for 24 to 96 hours. This is followed by a rise over the next seven to ten days to levels similar to those extant before pregnancy occurred.

Dr. Whitehouse: What were the levels of insulin before Mrs. C.'s pregnancy?

Dr. Solorio: She required no insulin.

Dr. Whitehouse: Therefore, she may not require insulin after delivery, correct?

Dr. Solorio: Certainly.

PREGNANCY AND DIABETES

Dr. Whitehouse: On the day of delivery, especially in patients undergoing a Caesarean section, we decrease the daily dose of insulin to the pre-gravid level, and then adjust it accordingly in the post-partum state. In our patient we probably will stop the insulin on the day of delivery and follow her response closely.

I should like to open the question-and-answer period with a question.

Dr. Jurgensen, what about the blood sugar levels of the new born baby?

Dr. J. Craig Jurgensen (Division of Metabolism): A recent review⁶ of 473 live-born infants of diabetic women indicated that these babies rarely manifested symptomatic hypoglycemia. Indeed, only one neonate presented symptoms which could be ascribed to hypoglycemia. Hypoglycemia, defined as a blood glucose below 20 mg. per 100 ml., occurred in only 12 per cent of 97 infants whose blood glucose was measured between one and 96 hours of age. This study suggested that a blood sugar level above 20 mg. per 100 ml. is sufficient for the metabolic requirements of the infant's brain. In children with levels below 20 mg. per 100 ml., intravenous glucose may prevent central nervous system damage.

Dr. Whitehouse: Dr. High, would you comment on this point?

Dr. High: Many infants born to diabetic mothers never have any difficulty with hypoglycemia. Some, however, rapidly develop symptoms. Blood sugars should be obtained at birth, at four hours and subsequently depending upon the clinical course of the infant. In addition, other metabolic problems may arise. Since some of these infants are also hypocalcemic, tetany may develop.

Dr. Whitehouse: Do premature infants have lower blood sugars than full term infants?

Dr. High: Yes.

Dr. Richmond W. Smith (Department of Medicine): Is there any delay in skeletal maturation in the baby of a diabetic mother?

Dr. Ayers: No. This has been well studied. Skeletal maturation is one of the most consistent things that one can find in any pregnancy complicated by any disease, including parathyroid disorders. A comment regarding the treatment of the diabetic mother with estrogen and progesterone is appropriate. There is a suggestion by some authors that these babies weigh less, though their length and head diameter is unchanged.

Dr. Whitehouse: The polemic regarding the use of supplemental estrogens and progesterone in the pregnant diabetic mother has stimulated great interest in diabetes and pregnancy. However, their use is not widely accepted. We do not advise supplemental hormonal therapy in our patients.

WHITEHOUSE

If there are no other questions, I would like to close with some words which were written 50 years ago by Dr. Elliott Proctor Joslin, late doyen of specialists in the field of diabetes, based on observations made by him between 1894 and 1916:⁷

"Conclusions upon pregnancy in diabetes: From a study of these cases, it would seem that the secret of success in the treatment of the pregnant woman with sugar in her urine would be to have the patient under constant supervision throughout the course of the pregnancy and for months and years after confinement, because it is not uncommon for the sugar to return." We certainly would not quarrel with that in 1966. "Treatment should follow exactly the same methods which are employed in the treatment of the usual case of diabetes, although a special pain should be taken to prevent the appearance of acidosis." We concur. "The advantages of a Caesarean section should be borne in mind. Ether anesthesia is not so safe as gas and oxygen; local anesthesia should be considered. Pregnancy in diabetes does not demand immediate abortion, even if acidosis is present." We agree with all of these comments. Then Dr. Joslin makes some very cogent predictions. "The next few years may show that pregnancy may take place in diabetic patients far more regularly than has been supposed." Ask any obstetrician and he will agree with this. "And it is certainly true that with the improvement in the treatment of diabetic patients, diabetic women will be less likely to avoid pregnancy." Ask any diabetic woman and she will agree.

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