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Classification of diabetes mellitus in pregnancy : with special reference to recent developments in pathophysiology and early detection

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THE CLASSIFICATION OF DIABETES MELLITUS IN PREGNANCY WITH SPECIAL REFERENCE TO RECENT DEVELOPMENTS IN PATHOPHYSIOLOGY AND EARLY DETECTION

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With the discovery of insulin by Banting and Best in Canada in 1921, the future of the diabetic was altered drastically. Within two years insulin was being prepared commercially for use in the treatment of human diabetes mellitus, and the plight of those afflicted with this metabolic error seemed suddenly quite optimistic. Even greater was the impact of this discovery on the practice of obstetrics; where, before the addition of insulin to the armamentarium of the physician, pregnancy in the diabetic was a tragic proposition often ending in spontaneous abortion or precipitating diabetic acidosis and coma and sometimes death. If the pregnancy continued to term, stillbirths were not uncommon nor were abnormal infants with multiple congenital anomalies including a strikingly high incidence of congenital heart disease as well as club foot, hydrocephalus, and abnormalities of the adrenal and thyroid glands. De Lee (1914)[16] expressed quite clearly the risks of pregnancy reporting that "abortion and premature labor occur in 33%.... The children, if pregnancy goes to term, often die shortly after birth, the total mortality being 66%.... Without a doubt pregnancy has a bad effect on the course of the disease...." He noted that maternal mortality was also adversely affected "...finding over 50% mortality, of which 30% died in coma, the others of tuberculosis or coma within two and one-half years." De Lee thus felt that "...if a woman comes under treatment with a history of diabetes, and the examination of the urine in the first months shows grape sugar, it is best to terminate the pregnancy at once." Foster (1915)[20] further emphasized these

views noting "pregnancy is correctly regarded as a great hazard...since the disease is sometimes rapidly progressive...or terminates in death.... The danger of pregnancy is comparable to that in patients suffering from tuberculosis and severe valvular disease." Infertility was also a major consideration, especially in the juvenile diabetic where Skipper (1933)[47] reported fertility to be as low as

With the utilization of insulin in the therapy of the diabetic mother, maternal mortality has decreased markedly and, in today's practice, has been essentially eliminated. In addition, in the well managed diabetic, infertility is now an uncommon complaint. Fetal survival has also improved; nevertheless, excessive fetal wastage still continues even with the application of a multiplicity of new principles of management which have evolved in the last four decades. Perinatal mortality still ranges between 15 and 30% with diabetic mothers, while the expected rate in the United States for all pregnancies is less that 5%.[¥] Even when most hazards are reduced to a minimum by vigorous prenatal care, the frequency of maternal and fetal complications, nevertheless, remains elevated as compared to that in nondiabetic pregnancies. Among such complications are habitual abortion, hydramnios, pre-eclampsia and eclampsia, prematurity, excessive weight gain, fetal macrosomia, antenatal and neonatal death, as well as multiple congenital malformations many incompatible with fetal survival.

Advances, however, continue to evolve in the management of the pregnant diabetic and in methods of early diagnosis of the disease entity itself. Three factors primarily are now almost universally stressed in the management of diabetes mellitus to improve fetal salvage, namely: (1) meticulous prenatal care; (2) delivery two to three weeks prior to the expected date of confinement; and (3) treatment of the newborn as a premature regardless of weight or gestational age. Today, the potential mother is carefully educated as to the difficulties which may be encountered during pregnancy and, when pregnant, is seen at frequent, regular intervals throughout the ante partum period. Cardiac and renal status are carefully evaluated early; and urines are generally tested daily by the patient, glucosuria being kept in rigid control through diet and the judicious use of insulin. Experience has also shown that if pregnant diabetics go to term, there is an increased risk of intrauterine fetal death. This knowledge has subsequently led to the induction of labor fourteen to twenty-one days prior to the EDC. Thus, through careful management, fetal survival as well as maternal well-being has been significantly improved in the recognized diabetic.

Several major problems continue to perplex the obstetrician, however, and include a mode for the ready and prospective recognition of the "potential" diabetic. In addition, an objective method of evaluating the status of the disease process based on its severity as related to the course of

the pregnancy is also an important point of debate as "there has been a gradual awakening to the fact that fetal loss in the so-called 'prediabetic' may approach that found in the frank diabetic."[42] For this reason "increasing attention has been directed at the association of pregnancy with the prediabetic state. Retrospective studies have shown...the incidence of fetal wastage increasing with proximity to the time of onset of clinical diabetes."[7] The prediabetic thus may well have some metabolic defect not marked enough yet to alter the glucose tolerance curve but which is detrimental to the fetal environment.

Boronow and McElin (1965)[5], on the other hand, suggest that prediabetes has no clinical significance for the fetus in utero and note that the only abnormality recorded in their twenty year series was macrosomia. They feel that complications of pregnancy noted in the past and associated with prediabetes were actually manifestations of a then undiscovered active diabetic process. Most authors, however, do not support this idea but instead continue to support the concept that prediabetes is associated with increased fetal risk which seemingly begins to increase in severity approximately five years prior to onset of a detectable abnormality in glucose metabolism. Whether these manifestations are in fact secondary to a failure to detect diabetes as suggested by Boronow and McElin or whether an actual metabolic disturbance is present in the prediabetic will have to await further investigation for clear evaluation.

Numerous investigators have attempted in the past to

utilize the many complications suggestive of diabetes mellitus in the apparent nondiabetic to predict the likelihood of diabetes appearing at some later time in the life history of the patient. As early as 1933, Skipper[47] suggested that the birth of a large baby might be indicative of the subsequent development of diabetes mellitus in the mother. Miller (1945)[34] noted that birth weight was often in excess of 4.5 kg. in the years prior to the clinical development of diabetes mellitus, Jackson (1952)[27] reporting that such large infants might be seen up to thirty years prior to the "clinical onset" of the disease. Pomeranze, Stone, and King (1959)[43] noticed a positive history of obesity in 88% of "prediabetic" patients during and following pregnancy. They too noted that the frequency of complications increased as the onset of overt diabetes mellitus approached.

Much care today must be taken in associating pathological reproductive conditions with diabetes, as a multiplicity of causes for fetal wastage and congenital malformations completely unrelated to diabetes mellitus are now known. While a definite relationship can be shown in many cases, to label patients with poor obstetric histories as prediabetic, even in light of a positive family history, would be somewhat presumptuous without first detecting some metabolic abnormality related to glucose or insulin metabolism.

TERMINOLOGY

Before proceeding further, an attempt to clarify several terms applied to the pregnant diabetic is in order as "the concepts of frank diabetes, chemical diabetes, gestational

diabetes, latent diabetes, prediabetes and their varying synonyms are and have been beclouded by lack of semantic clarity. Vague and variable overlapping exists,"[5] prediabetes especially remaining a "nebulous diagnostic entity."[7] In general, categorizing has been on the basis of some form of glucose tolerance testing, prediabetes referring to that period which antedates the appearance of an abnormal standard glucose tolerance curve. However, much confusion has been introduced into the literature by the misuse of this, as well as the other diverse terminology which has been applied to the diabetic process. In addition, much experimental evidence offered in the past may well be misleading as "it is easy to overlook detectable diabetes, for during this period the fasting blood sugar may be normal and random urine specimens may reveal no glucose.... There is almost always an interval of unrecognized diabetes in the life history of each diabetic"[29] that is not true prediabetes, when abnormalities of carbohydrate metabolism exist but are undetected without the use of specialized screening procedures. For this reason, Conn and Fajans (1961)[15] pointed out that there is as yet no way to diagnose prediabetes except in retrospect and thus defined "the prediabetic period as that interval from conception to the earliest demonstration of diminished insulin activity by whatever method is considered to be the most sensitive...,"[29] the "most sensitive method" being the key to their definition and thus clearly limiting the scope of this concept. Today, we might also, with the knowledge of recent discoveries in the pathophysiology of this disease,

delete "diminished insulin activity" and instead substitute "relative insulin deficit" to better express the true nature of this stage in pregnancy, because it is not truly diminished activity which marks the abrupt end of the prediabetic period and the "onset" of overt diabetes, but a relative inability to supply sufficient insulin to cope with the added stress of pregnancy.

Latent diabetes has often been confused with prediabetes in the literature but should be reserved for that interval of apparently normal carbohydrate metabolism following a period of distinctly abnormal carbohydrate tolerance which has developed under some type of stress. Since pregnancy is a period of stress for the individual and thus a diabetogenic event in the predisposed mother with a less than adequate capacity for insulin production, evidence of diminished carbohydrate tolerance may occur at some period of gestation, the likelihood increasing as term approaches. As all levels of impaired tolerance will be encountered, many asymptomatic cases will escape detection and have often undoubtedly been included in many series of "prediabetes" in the past, further confusing statistical evidence developed in earlier studies. The term "subclinical diabetes" and "gestational diabetes" have also been used synonomously with "latent diabetes" by many investigators and might well be deleted from the "diabetic glossary" to help clarify the semantics involved.

In an attempt to standardize terminology and thus hopefully help render studies more comparable, the World Health

Organization[58] in 1965 proposed the following definitions:

> Potential diabetes--The glucose tolerance test is normal; but the patient is the identical twin of a diabetic; or both parents are diabetic; or one parent is diabetic, and a close relative of the other parent is diabetic. In addition, gravidas having given birth to a child weighing over 4.5 kg., or who have had a stillbirth with hyperplasia of the pancreatic islets not due to immunological incompatibility are included.
>
> Latent diabetes--The individual has had a diabetic glucose tolerance curve at a time of stress or in response to a provocative test.
>
> Asymptomatic diabetes--A person with a diabetic oral glucose tolerance test and a fasting blood sugar below 130 mgm. %.
>
> Clinical diabetes--Patients with an abnormal glucose tolerance test, who have symptoms or complications of diabetes mellitus.
>
> Prediabetes--To be used only in retrospect to describe that period of time from conception to the diagnosis of an episode of diabetes mellitus.

These suggested definitions are, nevertheless, in some respects as inadequate as many proposed in the past. The category of "potential diabetes" is quite acceptable from a genetic point of view; however, the inclusion of several

specific pathological manifestations with the exclusion of others seems to be somewhat misleading in as much as either of these disturbances might well be produced by some other cause than diabetes, while those excluded might also be of equal prognostic value in predicting potential disease. The proposed definition for "latent diabetes," however, does follow quite closely the general pattern previously discussed. "Asymptomatic diabetes," on the other hand, seems to be an unnecessary category, such patients generally falling under the classification of "clinical diabetes," which in turn should include all those with abnormal glucose tolerance which appears at a time when the patient is not subject to "stress" per se. In addition, "prediabetes" as proposed by WHO is too broad in scope as can be seen from the foregoing discussion of this category.

CLASSIFICATION

Prior to 1949 no real attempt had been made at deriving a working classification of diabetes in pregnancy. Colwell (1947)[14] in a review of the subject simply divided diabetics in general into "mild" and "severe" subdividing severe diabetics into moderate, severe, and labile or brittle. In order to more precisely define the degree and severity of diabetes mellitus in pregnancy, circumvent some of the ambiguities in terminology, and thus be better able to evaluate over all therapy as well as prognosticate intelligently, White (1949)[56] undertook to classify diabetics on the basis of a combination of factors including family and obstetrical history, physical findings, and laboratory studies. Her

classification ranged from those patients in which the chance of fetal surivial was highest, i.e., "Class A," to "Class F" where both maternal and fetal risk were quite high. "Class A" diabetics were those in whom a diagnosis of diabetes was made on the basis of an abnormal glucose tolerance test, but who required no insulin and little dietary regulation for control of their disease. "Class B" included patients whose diabetes "started" in adult-life, i.e., at an age greater than twenty, who were free of any vascular disease which could be attributed to the diabetic state, and where the duration of the disease was less than ten years. "Class C" diabetics were those whose disease process had been of long duration, i.e., between ten and nineteen years with minimal vascular involvement and with an onset between ages ten and nineteen. "Class D" individuals had had diabetes for more than twenty years with an onset before age ten and had an even greater degree of vascular involvement. "Class E" patients exhibited calcification of the pelvic arteries on radiographic examination while those classified as "F" had nephropathy associated with their diabetes. In 1965[57], an additional class, "Class R," was added to delineate those diabetics with proliferating retinopathy.

White's classification was and probably still is the most widely used and accepted scheme even though quite artificial in some respects in light of recent findings concerning the pathophysiology of the disease process. Many authors have in fact found major faults in this scheme and have either attempted to modify it or to propose entirely new classi-

fications based on somewhat different precepts. Such schemes have been introduced based on the amount of insulin utilized by the patient, the age of onset and duration of the metabolic abnormalities, past obstetrical complications, and the presence or absence of sequelae of diabetes which may be deleterious to the mother, fetus, or both.

Pedersen and Pedersen (1965)[39] pointed out that at least in terms of perinatal mortality, the relative size of "Class A" and "Class F" of White's classification were the determining catagories of this statistic. They proposed the use of White's classification in combination with a series of "prognostically bad signs (PBSP)" which included hyperpyretic pyelitis; precoma or severe acidosis; toxemia; the neglector, i.e., the mother who is unreliable in controlling her diabetes; and hydramnios in the presence of any of the preceding complications. They felt that "the best prediction is obtained by combining White's classification with" their "PBSP classification, since the risk involved by a PBSP complication depends on the White's class in which it occurs.... The two systems supplememt each other, White's being based on factors present prior to the occurence of pregnancy, and PBSP on complications which become evident during pregnancy."

From their series, patients classified as "A" showed a perinatal mortality of 4.8% while those in "F" had 47.8%. Combining all patients in "B, C, and D" gave 17.4%. By introducing PBSP into the system, however, "Class A" diabetics without these manifestations showed no perinatal

mortality while those with PBSP had a level of 10%. In the combination of "B, C, and D" with PBSP, perinatal mortality rose to 32.0%, while in those without such complications it fell to 8.7%. In "Class F" mortality with and without PBSP was respectively 52.3% and 25.0%. By using PBSP it was thus possible to isolate a large group of pregnant diabetics (42.5%) with a high perinatal mortality (31.5%) while the mortality for infants with mothers without PBSP was less than half the average (17.9%). With PBSP and hydramnios, levels rose to 28.9% versus 14.3% in those pregnancies without hydramnios; while with hydramnios alone, the value was 6.7% versus an overall value without hydramnios of 8.3%. Horger, Keller, and Williamson (1967)[25] also add excessive maternal weight gain as a further PBSP but also note somewhat less striking but still significant differences than Pedersen and Pedersen in mortality between patients with and without PBSP when applied to the White classification.

Pedowitz and Shlevin (1955, 1964)[41,42] suggest in regard to the various modes of classification, that while insulin requirement is a good index of disease severity, fetal survival is related actually to the degree of control. In addition, "from an obstetrical point of view, it is the location of the arteriosclerotic change...as well as the duration of the metabolic disturbance" that determines the severity. They also support the observations of Pedersen and Pedersen that there is no difference in fetal salvage between classes "B, C, and D," but in the presence of nephropathy, marked retinitis, coronary disease, or

atherosclerosis especially of pelvic vessels, fetal loss and maternal risk are increased. They thus suggest that "pregnant diabetics should be divided into two groups, depending upon the presence or absence of degenerative sequelae of diabetes," and "propose that the term 'Class A' be eliminated, since it represents a heterogenous grouping, and that the patients formerly included under this heading be divided into two distinct categories based upon the alterations in carbohydrate metabolism during the pregnancy." "Class I" would include "all patients showing abnormal glucose tolerance on a test meal, who remain euglycemic on an unrestricted dietary intake throughout pregnancy" and thus have normal fasting and post-prandial blood sugars. "Class II," on the other hand, would include "patients who become frankly diabetic during pregnancy" who would thus have increased fetal risk similiar to the frank diabetic and, therefore, fall into the category of "latent diabetics" in as much as after pregnancy the disturbed carbohydrate metabolism generally would revert to normal in such individuals.

DIAGNOSIS

All classifications heretofore proposed still are quite arbitrary depending on a certain degree of clinical judgement and subjective interpretation and still do not provide a guide for detecting early diabetes but instead are applied generally in retrospect after the disease process has manifested itself in the hopes of providing better care at this point in the disease process. Singularly absent is a "class" for the early diabetic with a rational <u>modus operandi</u> for

discovering such individuals before insult has occurred to either the mother, infant, or both.

Traditionally, the diagnosis of diabetes mellitus has been on the basis of the four hour glucose tolerance test. However, in the last decade a multiplicity of variations of glucose tolerance testing have developed; and subsequently much controversy has arisen concerning their application and interpretation. Variations in technique *per se* have increased the confusion and have made comparison of results from various investigators very difficult if not essentially impossible in many circumstances.

O'Sullivan *et al.* (1966)[36] still support the oral glucose tolerance test as the mainstay of early diagnosis when administered during pregnancy and consider it to have a predictive value comparable to that of the cortisone primed test for nonpregnant individuals. They feel that an abnormal response to glucose during pregnancy ultimately signifies an abnormal outcome of pregnancy at some future time but note in their series, that over 97% of the women with an abnormal glucose tolerance test during pregnancy had nondiabetic values within six months after delivery. Because of the significant number, however, who subsequently were found to develop abnormal glucose tolerances, this category of patients was felt to be in a high risk group for future diabetes mellitus by these authors.

Many investigators, on the other hand, have pointed out that the alimentary disturbances of the puerperium may interfere with absorption of glucose and thus give aberrant

results, namely false negatives. Accordingly, these individuals recommend utilization of the IV glucose tolerance test. An additional advantage mentioned is that a single value can be calculated for disappearance rate, thus facilitating interpretation and comparison of values obtained assuming a standard procedure is utilized. However, it is also pointed out that the IV glucose tolerance test "may not be dependable for the detection of minor or even appreciable impairment in islet function. The greater and more sustained release of insulin..., may so overwhelm the mechanism of placental insulin degradation that the normal fall in blood sugar may occur despite functionally inadequate islets...." In addition, "...the low renal threshold...in pregnancy...may result in an unusually marked loss of glucose in the urine, sufficient to produce an artificially low blood sugar...."[2]

In addition, Benjamin and Casper (1967)[3] note that the oral glucose tolerance test when normal in pregnancy was 88% valid and when abnormal 89.4%. The IV glucose tolerance test, on the other hand, was 53% and 95.7% valid respectively. The oral glucose tolerance test when abnormal yielded 10.6% and the IV glucose tolerance test 4.3% false positive results; while when normal, the oral glucose tolerance test gave 12% and the IV glucose tolerance test 47% false negatives, thus revealing a major disadvantage in the use of the IV glucose tolerance test.

As Lunell (1967)[32] so aptly points out concerning the two tests: "Factors such as state of nutrition, infection, liver

disease, prolonged inactivity, steroids and salicylates are known to modify the test.... The variable factors of gastric emptying and intestinal absorption...add errors.... The IV glucose tolerance test...facilitates...statistical analysis...and makes it easier for comparison of results between different investigators provided the calculations were performed in the same manner.... It is, however, understood that the oral administration of glucose induces a different and more physiological response as the gastro-intestinal tract exerts an influence on glucose metabolism."

PATHOPHYSIOLOGY

If we accept the premise that "pregnancy may be considered as a diabetogenic event which is nevertheless survived without apparent diabetes by the great majority of women..."[29] then we must utilize a special set of criteria for interpreting glucose tolerance tests in the pregnant diabetic patient and not accept the values generally accepted for the nonpregnant individual. Gestation taxes maternal insulin reserves and thus in prediabetes may unmask the disease, while, in the unafflicted individual, it simply reduces reserves in a sense analogous to the cortisone primed glucose tolerance test. This analogy is, however, entirely too simple, because, as recent research has shown, a multitude of complex interactions are seen which reduce relative insulin reserve in the pregnant patient which would not be operable in the nonpregnant individual.

The pregnant state is generally believed to diminish

sensitivity to exogenous insulin, produce increased placental degradation of insulin, and lead to increased levels of insulin-like activity. "Regularly observed attenuation of decreases in plasma inorganic phosphate after carbohydrate loading or insulin administration permits the interpretation that decreased peripheral utilization of carbohydrate occurs late in pregnancy."[7] In addition, it has been noted that pregnant patients, especially in the last trimester, are resistant to the hypoglycemic effects of tolbutamide which is felt by some to be due to decreased insulin secretion in response to stimulation as a consequence of diminished insulin production and storage. This may well be an indication that pregnancy even in the "normal" individual taxes the pancreatic reserves markedly. Leake and Burt (1965)[30], however, do not feel that this hypoglycemia can be explained on the basis of diminished pancreatic storage or reduced production of insulin but offer no alternative explanation.

Bleicher, O'Sullivan, and Freinkel (1964)[4] also point out that the fetus contains enzymatic mechanisms for the proteolytic inactivation of insulin; and, in addition, maternal insulin has free access to the insulin degrading systems within the placenta. Spellacy et al. (1964)[51] support these findings but note that there is actually in fact little effective transfer of maternal insulin from mother to infant as the insulin is "trapped" by the placenta and rapidly degraded. As the placenta develops, the degree of insulin degradation increases, thus magnifying the relative

load on the mother as pregnancy advances. They thus suggest that there may actually be a placental block to insulin transfer, for while tagged insulin injected into the mother appeared on both sides of the placenta, levels were clearly independent of each other. Other possible explanations would include rapid placental destruction as previously suggested as well as heightened placental or protein insulin binding.

Hyperlipemia as seen in diabetes mellitus is also seen as a concomitant finding in the pregnant patient secondary to an abnormality of lipid metabolism. This disturbance is characterized by a failure of circulating insulin to lower the plasma concentration of non-esterified fatty acids which is normally seen in the nondiabetic after an overnight fast, where peripheral caloric needs are increasingly met by products of fat metabolism, endogenous glucose being spared to fulfill cerebral demands. Comparably efficient conservation of carbohydrates cannot, however, occur in pregnancy. "By virtue of the host-parasite relation between mother and conceptus, and the ready transplacental passage of glucose, amino acids, and perhaps even glycerol. pregnancy interposes additional structures for preempting maternal glucose and gluconeogenic precursors.... The action of insulin upon glucose utilization may be diminished whenever intracellular and extracellular free fatty acids are increased.... Thus, in the 'accelerated starvation' of pregnancy, more insulin could be required to maintain basal carbohydrate regulation just as basal insulin output might be increased through

heightened feedbacks via starvation products such as ketones."[4]

Experimentally, Bleicher, O'Sullivan, and Freinkel (1964) found glucose levels were higher post partum after administration of 25 gm. of glucose than they were ante partum, while the disappearance rate of glucose was the same. Insulin response during pregnancy, however, was greater; while absolute reductions of free fatty acids were similar. When, however, decrements in free fatty acids were expressed as a function of the fasting concentrations, the percentile reductions were less ante partum.

Various humoral insulin antagonists have also been noted during pregnancy including growth hormone, adrenocorticosteroids, and serum immune factors. Spellacy and Carlson (1966)[48] noted that in pregnant nondiabetic patients blood glucose is lowered at term while plasma insulin is elevated. One explanantion might be that there is an increased level of an insulin antagonist such as growth hormone or a placental growth hormone prolactin-like protein present. Burt, Leake, and Dannenburg (1966)[8] feel, however, that growth hormone is not significantly increased during pregnancy and thus provides little insulin antagonism. Recent observations, on the other hand, suggest that placental lactogenic hormone, which is chemically related to growth hormone, may produce insulin antagonism during pregnancy as well as be related to the hyperlipidemia often seen and the increased synthetic activity of maternal tissues which usually accom-

panies the pregnant state.

It has been postulated that possibly a posterior pituitary secretion might also be involved in insulin antagonism. Spellacy, Carlson, and Birk (1966)[49] studied this relationship and concluded that no significant change in blood glucose or plasma insulin was produced by either of the oxytocic preparations Pitocin or Syntocinon. Pitressin did produce a rise in blood glucose which was felt, however, to be secondary to a release of glucose from the liver.

Mestman et al. (1964)[33] studied the effects of cortisone during pregnancy. They found a twofold increase in biologic activity based on a potentiation of the effects of exogenous hydrocortisone, which further elucidates a source of insulin antagonism in the normal pregnancy. On the other hand, Buchler and Warren (1965)[6] point out that "estrogen induces a plasma alpha-globulin termed 'transcortin,' which binds cortisol firmly and renders it biologically inactive. This mechanism may account for blunting of the cortisol effect" in pregnancy mentioned by Mestman, thus protecting the organism at least partially against insulin antagonism from this source.

Spellacy and Carlson (1966)[48] suggested that since the placenta is "known to synthesize estrogen, progesterone and ...a growth hormone-like protein...one action...could be to split triglycerides and thus elevate the levels of circulating free fatty acids...." In this manner the Krebs cycle would be blocked thereby producing a relative insulin resistance.

It was also noted that the insulin patterns of pregnancy mimic the estrogen-progesterone patterns seen. Experimentally administering Enovid 10 mgm. (norethynodrel with mestranol) resulted in a higher mean blood glucose level in normals thus lending support to this precept. Glucose disappearance rate was also slower while mean insulin values were higher in the estrogen-progesterone treated group. Preliminary data suggested that the mechanism probably was simply direct hormonal stimulation of the pancreas such that hyperfunction resulted. Buchler and Warren (1965)[6] noted that after estrogen administration (diethyl stilbesterol 3 mgm. daily), the oral glucose tolerance test gave a two hour value in the diabetic range. The IV glucose tolerance test, on the other hand, was felt to be "normal" in nondiabetics. It was thus felt by these investigators that the effect produced was related to a change in absorption rather than any true diabetogenic effect. It was also suggested by this group, that since estrogen increases glycogen content in the liver of spayed animals, it could be possible that increased liver glycogen diverts to the periphery a glucose load presented to the liver via the portal circulation thus elevating peripheral blood glucose spuriously in the nondiabetic.

Gershberg, Javier, and Hulse (1964)[21] support these findings and add that the degree and incidence of abnormal glucose tolerance after estrogen administration was higher in women with a family history of diabetes mellitus. The actual mechanism was again not actually elucidated, but two possi-

bilities were proposed. Firstly, estrogen could stimulate pituitary ACTH secretion thereby potentiating the diabetogenic effects of adrenal corticosteroids; and secondly, there might be an increase in plasma protein binding of insulin which could render it inactive. Burt, Leake, and Dannenburg (1966) , however, felt that their observations were inconsistent with this possibility as biologic assay of increased insulin-like activity found in pregnancy had been found in the free rather than the bound fraction.

Today serum assay for insulin and insulin-like activity appears to be one of the most promising adjuncts to early diagnosis yet developed. Both hyperinsulinemia and increased insulin-like activity have been demonstrated during pregnancy. Bleicher, O'Sullivan, and Freinkel (1964)[4] found that paired individual comparisons of ante partum and post partum plasma insulin levels increased as pregnancy progressed. In addition, they found a greater release of insulin occurred in response to a glucose stimulus and postulated that certain insulin antagonists were in excess during pregnancy.[50] Spellacy et al. (1965)[53] reported that circulating plasma insulin in early pregnancy is only slightly increased, beginning to rise progressively with the progression of pregnancy. In late pregnancy the fasting level is higher than controls, and, in response to a glucose stimulus, a greater release of insulin occurs. Carrington and McWilliams (1966)[12] also found that higher levels of serum insulin were found at two and at three hours in patients whose genetic or obstetric backgrounds were sug-

gestive of diabetes. In these individuals the amount of insulin secreted was greater than that necessary to induce euglycemia in the normal gravida.

Specifically, "measurement of natural human insulin in the last month of pregnancy has shown elevated circulating insulin levels when compared to nonpregnant.... The measurable insulin rise above the fasting value after glucose stimulus was 3.0 times in late pregnancy and is 2.2 times in midpregnancy.... The possible sources are postulated as being either the maternal pancreas, the placenta, or the infant pancreas...,"[52] the maternal pancreas, however, being thought to be the actual source as suggested by the finding that maternal islets are hypertrophied in a normal pregnancy.

The excess insulin is postulated firstly to be secreted to counteract the increased amounts of an insulin antagonist such as growth hormone or a similar substance. "This substance is present in the syncytiotrophoblast cytoplasm of placental villi by the twelfth week of gestation. In addition, as previously noted "...there appears to be a decreased ability of the peripheral tissues to use insulin...." This would, therefore, "...require that more insulin be present in order to maintain the same peripheral effect." It is thus felt that "...the normal woman has a pancreas which begins to hyperfunction at least by midpregnancy and the output of insulin increases until the end of gestation...."[52] In addition, renal clearance of insulin is

lowered concomitantly to help maintain the hyperinsulinemia required to maintain normal carbohydrate metabolism in pregnancy.[54] As studies with estrogen-progesterone combinations show that these hormones stimulate the pancreas with subsequent hyperfunction, it is quite possible that this mechanism may well be an important signal for the hypersecretion seen in a normal pregnancy.

The prediabetic would thus ultimately present with signs of insulin deficiency, when the insulin supply was inadequate to meet the added demands of pregnancy in which excess insulin is necessary for a successful outcome. It is, therefore, conceivable in the very near future with further elucidation of the mechanisms inherent to insulin and glucose metabolism in the pregnant state, to be able to demonstrate by direct assay of the components involved, an abnormality of metabolism indicative of diabetes mellitus well in advance of the development of overt complications.

CONCLUSION

Terminology as applied to the diabetic patient in obstetrics today is fraught with much ambiguity and overlapping, the specific bounds of the categories being only loosely defined. Terms are often quite freely interchanged by many authors as semantics seemingly vary as do also the limits placed upon these classes. For this reason, in light of recent developments in the pathophysiology of this disease process, clarification of these terms with special emphasis on the limitation of their scope is needed to

alleviate much of the confusion in usage which is found in the literature and, in this manner, establish a basis for comparison of studies in the future.

The term "prediabetes" should be reserved for that interval from conception to the earliest demonstration of a relative insulin deficit through the utilization of the most sensitive method available. "Potential diabetes," on the other hand, should include all those genetically predisposed, i.e., the sib of an identical twin who is diabetic, or the daughter of parents who are both diabetic, or where one parent is diabetic and a close relative of the other is diabetic. The application of disturbances of the course of pregnancy or of the development of the fetus such as macrosomia, habitual abortion, hydramnios, or recurrent congenital anomalies as indicators of potential disease is also of value; but caution must be exercised in such usage, as a great diversity of causes for these disturbances exist entirely unrelated to diabetes mellitus. "Latent diabetes" should indicate that period of apparently normal carbohydrate metabolism following an episode of distinctly abnormal carbohydrate tolerance which has appeared secondary to some type of stress. Only one other category should be required to complete this spectrum of definitions, namely "clinical diabetes," where an abnormality of glucose or insulin metabolism can be demonstrated by any means available without the concomitant production of "stress" and with or without the presence of any other signs or symptoms of the disease process. The many other terms such as

asymptomatic, gestational, stress, or subclinical diabetes represent redundant subdivisions tending only to confuse discussions and, therefore, should be eliminated from general use.

In addition, difficulties have also arisen surrounding the classification of diabetes mellitus when present during pregnancy. Classification, while still somewhat artifical in basic design, should until a more precise and "physiological" plan is available based on prospective evidence continue to be based on the original precepts of White (1949)[56] with, however, the further subdivision of each class by the presence or absence of various prognostically bad signs as originally proposed by Pedersen and Pedersen (1965)[39]. In this manner, it should be possible to further improve prognostication and therapeutic planning, as it has been clearly shown that the presence of many of the obstetrical complications of diabetes mellitus including hyperpyretic pyelitis, precoma or severe acidosis, toxemia, and hydramnios as well as the poorly controlled patient and possibly excessive weight gain, add greatly to morbidity.

To reiterate, "Class A" included all those with abnormal glucose tolerance requiring no insulin and only minimal dietary regulation. "Class B" patients developed diabetes after age twenty, were free of vascular disease attributed to diabetes, and had the disease less than ten years. "Class C" diabetics had been afflicated for more than ten years but less than nineteen years with an onset between

the ages of ten and nineteen and with only minimal vascular involvement. "Class D" individuals had the disease for more than twenty years with onset before age ten and with vascular involvement greater than that seen in "Class C." "Class E" included individuals with calcification of the pelvic arteries demonstrable radiographically. "Class F" diabetics also showed nephropathy, while those in the newly formed "Class R" exhibited proliferating retinopathy.

In addition to these seven classes, two additional groupings should be added. one to include potential and the other latent diabetics. The latent diabetic has already manifested some abnormality of glucose or insulin metabolism which could quite possibly progress under the stress of pregnancy. On the other hand, the potential diabetic might well note the first clinical expression of disease in response to such stress. In both cases it is conceivable that the many complications of pregnancy attributed to diabetes might appear if an increase in insulin requirement could not be met in such a predisposed individual. For this reason delineation of these two groups is a necessary aide in rationally planning the regimine of such patients during their pregnancy to hopefully decrease potential morbidity by being alerted to the possiblity that overt diabetes could appear.

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