Maternal Vascular Disease and Fetal Growth

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Maternal vascular diseases are known to influence fetal growth by reducing the availability of nutrients through the impaired uteroplacental circulation. Intrauterine fetal growth retardation (IUGR) is related to an increased risk for perinatal morbidity and mortality. The etiologic factors that result in IUGR are generally difficult to identify. A distinction can be made between intrinsic and extrinsic factors that cause the restriction of fetal growth potential (Table 1), but in many fetuses IUGR is defined as idiopathic or asymptomatic, as none of the identifying factors can be shown to be responsible for the process. Gestational hypertension and the chronic diseases that affect the maternal placental circulation are the principal factors in IUGR (50% to 60%); chromosomal disorders and congenital anomalies are reported in 5% to 10% of all cases of IUGR, and fewer than 10% may have impaired intrauterine growth secondary to congenital infections (1).

In this chapter, we focus on some findings that seem to open new strategies in the identification and treatment of fetal growth retardation: the possibility of monitoring an increased maternal blood pressure in patients with asymptomatic fetal growth retardation; determination of the relations between maternal hyperinsulinemia and reduced fetal growth; and treatment with intravenous immunoglobulin (IVIG) to reduce the incidence of fetal growth retardation in patients with antiphospholipid antibodies.

ASYMPTOMATIC FETAL GROWTH RETARDATION AND INCREASED MATERNAL BLOOD PRESSURE

The asymptomatic growth-retarded fetus (aIUGR) is one in the left part of the overall birth-weight distribution curve, or whose growth is affected by sex, birth rank, race, or maternal height (2). Recently, the use of portable, noninvasive, 24-hour ambulatory devices to monitor blood pressure has been shown to be harmless and effective in defining maternal pressure parameters (3). As a result, different parameters have been adopted. Our objective was to investigate maternal blood pressure with a portable, automatic 24-hour device after the diagnosis of aIUGR had
been made ultrasonographically, and to assess the possible role of an undiagnosed hypertensive status in the etiology of growth retardation.

Singleton pregnancies with a first-trimester ultrasonographic scan to assess correct gestational age were included in the study once ultrasonographic diagnosis of fetal growth retardation had been made. Gestational age was above the 28th week, and fetal abdominal circumference below the 10th centile for gestational age for our growth curves, with evidence of a decline across the growth centiles. Identified or suspected gross fetal anomalies, positive immunologic response to any infectious disease (toxoplasmosis, rubella, cytomegalovirus infection), and any chronic or hypertensive disease of the mother were considered to be exclusion criteria. In the week following the ultrasonography and Doppler evaluation, we recorded maternal blood pressure with two portable automatic devices. SpaceLabs 90207 was programmed by a DOS-PC through specific hardware, SpaceLabs 90209 (SpaceLabs Inc., Redmond, WA, USA). Ambulatory recordings were obtained by oscillometry every 30 minutes from 08.00 to 20.00 and from 20.00 to 08.00 during 24 hours, for a total of 50 recordings. The data obtained were analyzed at the end of the 24-hour recording. To describe the whole maternal blood pressure regimen, we chose the mean 24-hour diastolic blood pressure (DBP). This index was recently used as a specific predictor of pregnancy hypertension and pre-eclampsia (4). Four different groups were formed for comparison with the results obtained in the aIUGR group: (a) gestational hypertension with IUGR. Gestational hypertension was defined, after Davey and MacGillivray (5), as a recording of diastolic blood pressure higher than or equal to 90 mm Hg on two consecutive occasions 4 hours or more apart in previously normotensive nonproteinuric women after 20 weeks’ gestation; (b) pre-eclampsia with IUGR. Pre-eclampsia was identified when gestational hypertension and significant proteinuria (>300 mg/24 h) were present; (c) gestational hypertension without proteinuria and without IUGR; (d) normotensive patients with normal fetal growth matched for gestational age (control group).

The results obtained in the evaluation of the mean 24-hour DBP are presented in

| TABLE 1. Etiologic factors in intrauterine growth retardation |
|-------------------|-------------------|
| **Intrinsic factors** |
| Chromosomal abnormalities |
| Congenital malformations |
| Genetic heritage |
| **Extrinsic factors** |
| Fetoplacental infections |
| Placental disease |
| Anomalous placentation |
| Maternal vascular disease |
| Maternal cardiopulmonary disease |
| **Unknown factors** |
MATERNAL VASCULAR DISEASE AND FETAL GROWTH

FIG. 1. Mean value of maternal diastolic blood pressure measurements after 24-hour automatic blood pressure monitoring in patients with asymptomatic IUGR (aIUGR) compared with controls, patients with gestational hypertension (GH), patients with gestational hypertension and IUGR (GH IUGR), and patients with pre-eclampsia (PE). The value for diastolic blood pressure was higher in patients with aIUGR than in controls ($p < .05$, Student's $t$ test) but did not differ from that in patients with GH (NS).

The highest mean 24-hour DBP value was found in the pre-eclampsia group (84.1 mm Hg). This result does not differ significantly ($p = .38$) from the value obtained in the gestational hypertensive group with IUGR (81.09 mm Hg). The aIUGR group showed a mean 24-hour DBP value of 68.3 mm Hg, which was higher than that in the control normotensive group (61.9; $p < .001$), and lower than that in the gestational hypertensive group without IUGR (75.1 mm Hg; $p < .005$).

Five fetuses had an umbilical S/D (systolic/diastolic) ratio above the S/D cutoff value of 2 for gestational age, whereas PI (pulsatility index) values were all within the normal range. One fetus had a mean cerebral artery PI value above the normal range. Seven patients (38.8%) had an abnormal median uterine resistance index.
value. A diastolic notch was found in one patient bilaterally and in three patients unilaterally. Our results show that the mean 24-hour DBP value was higher in the aIUGR group than in the control group. Nevertheless, 16 of the 18 patients had a DBP value above the mean value for the normotensive group (61.5 mm Hg), and the two patients who had a normal DBP value had a normal uterine resistance index.

Comment

The condition of an isolated and asymptomatic IUGR fetus is usually defined as idiopathic because of lack of knowledge about the pathophysiologic processes that induce fetal growth retardation. The results obtained in the present series show a significant increase in mean 24-hour DBP in the aIUGR group vs. the normotensive control group. Moreover, almost 90% of the patients with an aIUGR fetus showed a mean 24-hour DBP value above the mean of the control group. Hence, in cases of isolated IUGR we recommend a complete evaluation of maternal blood pressure values by 24-hour blood pressure monitoring. The hypothesis that in these patients an incorrect placentation process might lead to a reduction in fetal growth potential rather than to the clinical presentation of maternal hypertension has already been reported by our group (6). The finding that 39% of IUGR fetuses had a high uterine resistance index and an increased mean 24-hour DBP value may provide evidence of an intermediate abnormal implantation process, resulting only in the restriction of fetal growth without the appearance of clinically evident hypertension in the mother. The distribution of abnormal uterine resistance index values in aIUGR infants found in this series overlaps values obtained previously with uterine Doppler resistance index as a screening test for gestational hypertension and IUGR (7). Recent reports (8) have underlined the correlation between abnormal Doppler findings in the uteroplacental circulation and the clinical appearance of hypertension or IUGR. The worst condition of the uterine circulation (bilateral notch and resistance index or PI above the 95th centile for the population studied) is more often linked with pre-eclampsia and IUGR than with isolated IUGR. Ducey et al. (9), in their classification of hypertension in pregnancy based on Doppler velocimetry, found only 12 patients among 136 hypertensive women with abnormal uterine and normal umbilical Doppler results. Although differences in peripheral vascular findings in IUGR fetuses have been described using Doppler evaluation both as a screening test and as a diagnostic test (10), no fetuses with absent end-diastolic flow in the umbilical artery were present in this group. This ominous sign in the small-for-gestational-age (SGA) fetus is more commonly detected at earlier gestational ages and in association with pre-eclampsia.

In the presence of fetal growth retardation with normal umbilical Doppler flow measurements, the main advantage in using 24-hour monitoring of maternal blood pressure is to obtain repeated measurements, which are more reliable than the traditional measurements. The use of this technique in patients with aIUGR and normal umbilical PI could then be helpful in the objective quantification of maternal blood
pressure. In our series, we found increased maternal blood pressure values in aIUGR pregnancies, equivalent to those of gestational hypertensive patients without IUGR and higher than those of normal patients. Confirmation of our observations by ongoing multicenter clinical trials would allow a new classification of aIUGR fetuses—those suffering from a limitation of growth induced by or complicated by an increase in maternal blood pressure without clinical hypertension. The diagnosis of idiopathic IUGR could then be confined to those fetuses with a reduced rate of growth and normal umbilical and uteroplacental Doppler and mean 24-hour DBP values.

MATERNAL INSULINEMIA AND HYPERTENSION AND FETAL GROWTH RETARDATION

It is well-known that in normal pregnancy insulin secretion increases throughout gestation, whereas peripheral insulin sensitivity decreases (11). Insulin resistance is believed to be the common feature linking hypertension and hyperinsulinemia. The presence of high maternal blood pressure is associated with impaired glucose tolerance and a lower birth weight (12). An increased insulin secretion with insulin resistance and a high insulin-to-glucose ratio may be a predictor of lower birth weight (13). We designed an experimental model to investigate the relation between maternal insulinemia and the glucose-to-insulin ratio in an asymptomatic population, and the subsequent development of gestational hypertension and IUGR. The study was conducted with an asymptomatic population of patients during the second trimester of pregnancy. Patients were submitted to an oral glucose tolerance test, with evaluation of basal and postloading insulinemia. Human placental lactogen was evaluated in the same basal blood sample. Patients were followed using normal procedures until delivery. The longitudinal protocol was based on an ultrasonographic evaluation at 33 to 34 weeks of gestation, and a clinical evaluation of maternal blood pressure and proteinuria every 15 days; 131 patients were then considered for the study. Median maternal age was 30.2 years (SD 3.4; range, 21 to 43). Median gestational age at the time of oral glucose tolerance test was 28.2 weeks (SD 3.1; range, 15 to 39). Median birth weight was 3050 g (SD 345; range, 1800 to 4050). Body mass index (BMI) was calculated as the ratio of weight to the square of the length. Mean BMI was 23.7 (SD 4.7; range, 16 to 41). Patients were divided according to oral glucose tolerance test results into three groups: (a) normal patients (n = 83, 63.3%); (b) patients with gestational diabetes (n = 19, 14.5%); (c) patients with impaired gestational glucose tolerance (IGGT) (n = 29, 22.1%). IGGT and gestational diabetes patients had values of glycemia at 60 minutes and 120 minutes that were higher than in the control group (p < .001). Basal insulinemia was significantly higher in the IGGT and gestational diabetes group than in the control group. A significant difference in BMI was present (p < .001), with the lowest values in the normal group. Human placental lactogen values did not differ among the three groups of patients, although the IGGT group had the highest values.
Birth weight was significantly higher in the IGGT group than in the normal group. In the patients with gestational diabetes, birth weight was not different from that in the normal group.

All the fetuses with isolated IUGR had normal oral glucose tolerance test results. Patients in whom isolated gestational hypertension developed were found in the normal oral glucose tolerance test group (50%) and in the IGGT group (31%). Gestational hypertension and IUGR were present in eleven patients in the normal oral glucose tolerance test group (78.5%) and in three from the gestational diabetes group. Patients with IUGR had 60-minute insulinemia and insulinemic area-under-curve values that were higher than those in controls. The median values of glycemia and insulinemia obtained in the IUGR and gestational hypertension patients with normal responses to the oral glucose load were then compared with those from the normal group: insulinemia at 60 minutes and 120 minutes was significantly increased in the former groups ($p < .05$) (Fig. 2).

**Comment**

The normal range of maternal plasma insulin in pregnancy is too wide to be useful in identifying hyperinsulinemic patients reliably. Our normal population showed a median level of basal insulinemia of 8.2 mU/l. Patients with gestational diabetes or IGGT showed higher levels of glycemia and insulinemia than did the control group.
Nevertheless, patients with normal responses to the oral glucose load in whom gestational hypertension or IUGR later developed had evidence of increased levels of insulinemia at 60 minutes and 120 minutes after the glucose challenge.

The state of increased insulin resistance, and therefore hyperinsulinemia, could lead to hypertension during pregnancy by several mechanisms, such as retention of sodium and water, activation of the sympathetic nervous system, decreased Na\(^+\)/K\(^+\)-ATPase activity, increased Na\(^+\)/H\(^+\) pump activity, increased cellular accumulation of calcium, and stimulation of growth factor receptors. In nonpregnant women, high blood pressure is prevalent in both obesity and diabetes, conditions associated with insulin resistance; essential hypertension is considered to be an insulin-resistant state (14). Ferranini et al. (14) noticed that insulin resistance involves glucose metabolism, is located in peripheral tissues, and is directly correlated with the severity of hypertension. Sowers et al. (15) found that women in whom pre-eclampsia developed showed insulin resistance (increased fasting insulin-to-glucose ratios) and abnormal intracellular free calcium metabolism as early as the second trimester of pregnancy. Abnormalities in cellular Ca\(^{2+}\) have been observed in women with gestational hypertension (11). These abnormalities include both decreased plasma membrane Ca\(^{2+}\)-ATPase activity and abnormal Ca\(^{2+}\) responses to vasoactive agonists. Insulin blocks vasoactive receptor and voltage-mediated Ca\(^{2+}\) currents in vascular smooth muscle cells, resulting in cell membrane hyperpolarization (15). Insulin also stimulates plasma membrane Ca\(^{2+}\)-ATPase and Na\(^+\)/K\(^+\)-ATPase activity and expression. Insulin-resistant states are associated with decreased plasma membrane Ca\(^{2+}\)-ATPase activity, increased Ca\(^{2+}\), and hypertension. The risk for IUGR increases if hypertension and hyperinsulinemia are combined (16). This is probably the result of placental vasculopathy, with reduced or impaired microvascular circulation (16). Solomon et al. (17) showed that hypertension in pregnancy occurs in the third trimester, when insulin resistance is greatest. They also noticed that insulin levels measured at the time of oral glucose tolerance test in a subset of women tended to be higher among women in whom hypertension developed during pregnancy. The same results were described with an association between hyperinsulinemia and raised blood pressure during the third trimester of pregnancy (13). Insulin resistance has been related to the development of hypertension, hyperinsulinemia, and increased insulin-to-glucose ratios. The raised blood pressure could be a direct mechanism responsible for the reduced fetal growth. Bevier et al. (12) found that within the group of women with gestational diabetes who required insulin, blood pressure and BMI correlated significantly with insulin resistance, quantified by the amount of insulin required to achieve glycemic targets comparable with those achieved in the diet-alone group. In addition, the administration of insulin was accompanied by a significant increase in blood pressure. Patients with normal response to the oral load in whom an IUGR fetus later develops have normal levels of glycemia with increased insulinemia. These two factors might contribute to a chronic state of reduced availability of glucose transferred through the placenta. Decreased availability of maternally derived glucose is responsible for diminished plasma glucose and insulin concentrations in growth-retarded human fetuses (18). Fetal hypoglycemia and hypoinsulinemia are major factors retarding fetal growth; a maternal hyperinsulinemic state
can result in maternal and fetal hypoglycemia and hence fetal growth retardation (19). Glucose is a primary fetal metabolic substrate and insulin is a key growth-stimulating hormone that has mitogenic and numerous anabolic effects (18); Breschi et al. (13) found that insulin area under the curve and the ratio of insulin to glucose area were inversely related to birth weight. The inverse correlation was also present in lean mothers, indicating that the link is not forced by obesity. There seems to be an association between maternal hyperinsulinemia and neonatal weight (13). Whether the hyperinsulinemia/insulin resistance is itself a cause of early fetal malnutrition or simply a marker for some underlying mechanism remains to be tested. Moreover, there has been recent interest in the association between intrauterine growth failure and the incidence of hypertension, cardiovascular disease, and syndrome X in adult life (insulin resistance, non-insulin-dependent diabetes, and lipid disorders) (20). It is therefore important to evaluate insulinemia after the oral load to characterize risk factors for the subsequent development of hypertension or retarded fetal growth. We recommend that maternal insulin levels be evaluated both in the fasting state and after a glucose load to characterize patients at risk for hypertension or IUGR.

ANTIPHOSPHOLIPID ANTIBODIES: ROLE OF TREATMENT IN MATERNAL DISEASE AND FETAL GROWTH RETARDATION

Autoimmune factors are recognized to play a role in recurrent pregnancy wastage and obstetric complications (21), even in women with no clinically diagnosed autoimmune disorders. Antiphospholipid antibodies are associated with fetal distress and fetal death. Pre-eclampsia (51%) and severe early-onset pre-eclampsia (27%) have been reported recently in these patients (22). The incidence of fetal growth retardation varies between 30% and 60% of reported cases (23).

Pregnancy complications vary according to the different therapeutic regimens used (corticosteroids, heparin, low-dose aspirin alone or in combination) (22,24,25). The use of high-dose IVIG for preventing recurrent spontaneous abortions and pregnancy complications has been reported in single cases or in small series (26). We have reported normal fetal growth in patients with antiphospholipid syndrome treated with high-dose IVIG (27).

In our series, 14 patients with primary antiphospholipid syndrome received treatment with high-dose IVIG. Ultrasonographic measurements of fetal growth obtained in the group treated with IVIG showed a biparietal diameter below the 10th centile in 23.2% (20/86), but the evaluation of head circumference reduced this to 6.9%. Abdominal circumference below the 10th centile was present in 2.3%, whereas in 90.6% (78/86) the abdominal circumference value was above the 25th centile. The data were assembled for 2-week intervals and compared with the control group. Head circumference was increased in the IVIG group at 36 to 37 weeks (p <.001), whereas no significant differences were present at earlier gestational ages. Abdominal circumference was increased in the IVIG group (p <.05) in the same weeks of
Abdominal Circumference

FIG. 3. Scattered reproduction of the values of abdominal circumference observed in the evaluation of fetuses from patients with primary antiphospholipid antibody syndrome treated with IVIG. Normal references are presented as continuous lines. No significant reduction in abdominal circumference values was observed in the studied group.

observation (weeks 36 to 37). No significant reduction of fetal abdominal circumference was seen in the treated group compared with the control group (Fig. 3).

Comment

The possibility that immunoglobulin infusions might play a role in the normal evolution of fetal growth should be considered. The type and extension of the placental lesions described in the antiphospholipid-positive patients seem to be of great importance for the availability of fetal nutrients. Placentae from women with adverse pregnancy events in the presence of antiphospholipid show extensive infarction (28), and decidual vasculopathy, placental thrombosis, and infarction are described as major factors in the pathogenesis of fetal growth retardation, intrauterine death, and maternal complications. High titers of antiphospholipid antibodies during pregnancy
show greatest sensitivity in predicting placental insufficiency and fetal death, whereas evidence of positive lupus anticoagulant is reported to have the greatest specificity. Moreover, placentae of antiphospholipid-positive patients show an unusual vasculopathy that includes not only histologic evidence of intravascular coagulation, fibrin deposits, and absence of tissue plasminogen activator and thrombomodulin but also endothelial swelling and infiltrates (29). A study of placental abnormalities in women with fetal death showed that those with antiphospholipid antibodies had an increase in placental fibrosis, number of hypovascular villi, and occurrence of thrombosis and infarction, fibrinoid necrosis, and obliterator endocapillaritis. There were no signs of inflammation (30). These features were absent in a control group made up of antiphospholipid-negative patients with fetal death. Milder placental histologic abnormalities are found in antiphospholipid-positive patients with liveborn or growth-retarded fetuses. For these reasons, the reduction of fetal growth and of the normal anabolic functions in these patients can be correlated with a direct reduction of placental transfer of nutrients resulting from structural defects induced by the actions of the antiphospholipid antibodies. Several therapeutic regimens have been tried in the past in pregnant women with unexplained autoimmune recurrent fetal loss. These treatments have not always prevented fetal growth retardation or fetal death. Out et al. (30) reported IUGR in 24% and intrauterine fetal death in 12% of 59 pregnancies positive for antiphospholipid. Three fetal deaths were present among the 11 pregnancies with persistence of lupus anticoagulant, and treatment with high doses of prednisone could not avoid the reduction in fetal growth observed. Branch et al. (22) reported a 43% incidence of fetal growth retardation among 23 patients with antiphospholipid antibodies treated with prednisone and low-dose aspirin; 20% in the group treated with heparin and low-dose aspirin; and 22% in the group treated with prednisone, heparin, and low-dose aspirin. The normal fetal growth reported in our series of antiphospholipid-positive patients treated with IVIG is therefore unusual in the natural history of these patients, and IVIG should not necessarily be considered as the therapeutic solution to this problem. However, we thought it important to present the results obtained on fetal development with IVIG. Although there is the possibility of a "casual" relation, IVIG efficacy is probably a consequence of the presence of anti-idiotypic antibodies in the preparations. It is well-known that these antibodies manipulate the immune system in at least three ways. First, they can neutralize an autoantibody by forming an idotype/anti-idotype dimer; then the anti-idiotypic antibodies may bind and down-regulate the B-cell receptor for antigen, decreasing the autoantibody production; finally, regulatory T cells may recognize anti-idiotypic antibody, and a critical concentration of idotype/anti-idotype dimers may then be required to activate binding and subsequent suppression through lymphokine production. Furthermore, the beneficial effect of IVIG in patients with autoantibodies might be a result not only of the described mechanism of passive transfer of neutralizing anti-idiotypic antibodies that act against the autoantibodies, but also of the modification of the structure, function, and dynamics of the idiotypic network so that the physiologic control of autoimmunity could be restored and brought to normality. If these are the hypothesized pathways whereby IVIG treatment exerts its positive effects on placental endothelial
function and hence on fetal growth, we could in the future regard IVIG therapy as "immunorestoration" of normal function of the network in patients affected by immunologic disorders.

REFERENCES


**DISCUSSION**

**Dr. Soothill:** You described your combination of Doppler and 24-hour blood pressure monitoring in predicting outcome, but did your gestational hypertension group have to have proteinuria as well? Because if not, I feel a bit worried about predicting hypertension by blood pressure, because that’s self-fulfilling, isn’t it?

**Dr. Valensise:** The problem is that when they had this measurement made at 24 to 25 weeks of gestational age, they did not have evidence of clinical hypertension, so the problem is to find something that could measure what is going on in the mother in a way that could be much more objective than a single measurement. I do agree with your point. If the mother is already hypertensive, there is no need to predict that she will become hypertensive. But the problem is that there may be differences in how the patients will appear in your hands or in my hands on the same day or on two or three different days. That method allows you to have a kind of objective centimeter, as we call it, to which we could refer to categorize a patient and to identify the risk, nothing more than that.

**Dr. Soothill:** You had a very interesting group—the normal small babies with hyperinsulinemia in the mothers. At what gestational age was that?

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**Dr. Soothill:** You had a very interesting group—the normal small babies with hyperinsulinemia in the mothers. At what gestational age was that?

**Dr. Valensise:** The median value is 31.2 weeks, so they are patients who are already in the third trimester. These were very late growth-retarded babies, referred because of suspected growth retardation.

**Dr. Battaglia:** We keep hearing about normal small babies, and I don’t think we should use that term until we know they are normal. Doris Campbell mentioned the other day that we have no follow-up data as to whether these children end up with central nervous system problems later on. I don’t know whether they are normal, and I am quite sure no one else knows whether they are normal. Secondly, you said that when you used that term, you were referring to a group of small babies, but did you follow them in the pregnancy, and is it true that they never developed abnormal velocimetry in the fetal vessels?
Dr. Valensise: We could not categorize the babies in exactly the same way as was done by Professor Pardi's group. "Normal small" was a definition to attract attention and nothing more. I still believe that these are babies who need to be followed. In our group a small percentage, about 10%, had an abnormal Doppler. I think that we must include both the umbilical Doppler and the uteroplacental Doppler. I think we should include information from both the maternal side and the fetal side.

Dr. Stuart Campbell: I don't think you could ever call a small fetus "normal small" if there is any abnormal Doppler. And indeed I think you mentioned that many of them had abnormal uterine Doppler, and as soon as you have an abnormal uterine waveform you have to classify that SGA fetus into some sort of category that implies impaired uteroplacental perfusion. So I think "normal small"—if you are ever going to use that expression—means that from all your investigations, you believe that it is a normal, genetically small fetus for normal genetic reasons. I would agree with Professor Battaglia that this is really a retrospective diagnosis.

Dr. Ogata: I am intrigued by your hypothesis about the insulin resistance. There are reports of syndrome X (insulin resistance and hypertension in gestational diabetes), but in that system the insulin resistance results in excess glucose coming across and an increased risk of macrosomia. So if I understand what you are saying, in this particular system you have insulin resistance that overcomes your hyperinsulinemia. Is that right? In one application of this model you can end up with a big baby, and in this application you are reducing glucose availability to the fetus and thus contributing to growth retardation.

Dr. Valensise: This is not my hypothesis, but one that has been presented in the literature. The problem is to try to subdivide the maternal metabolic adaptations, because in gestational diabetes you may find hyperinsulinemia but you may also find normal insulinemia in response to the oral glucose tolerance test. The hypothesis is that maternal hyperinsulinemia could lead to reduced availability of glucose from the maternal side to the fetal side, and this could result in chronically reduced availability of glucose to the fetus, followed by hypoinsulinemia in the fetus and reduced fetal growth. Of course, the pathway can't be that easy, and there must be something else going on—and I refer to all the interactions with the other factors affecting fetal growth. Still, I think it is interesting that some patients who don't show an abnormal response to the oral load and have normal levels of glycemia have levels of insulinemia that are 10-fold those of "normal" patients, and we don't understand why.

Dr. Stuart Campbell: I find it extraordinary that you could have a normal glucose tolerance test and maternal hyperinsulinemia. Could somebody explain that?

Dr. Godfrey: David Phillips from our metabolic programming group in Southampton has done statistical modeling of glucose tolerance tests in individuals in whom insulin resistance and insulin secretion have been specifically measured. My reading of the figure that you showed is that there wasn't fasting hyperinsulinemia but there was an exaggerated insulin response during the glucose tolerance test, and although you would need to apply these statistical models to the data, I would be very surprised, indeed, if those came out showing insulin resistance as opposed to exaggerated insulin secretion. I think there is a further danger in all this, in that we and others have shown profound intergenerational effects on fetal growth and further that men and women who had low birth weights may have a 10-fold increase in syndrome X as adults. So I think we have to be very careful about whether we are looking at intergenerational effects or specific effects relating to placental lactogen or whatever.

Dr. Valensise: I agree with you. Still, when we were looking for hyperinsulinemic patients for the first part of our studies on the receptor, we could find a cutoff value, and the fasting values of insulinemia in literature range from 8 to 25 μU/l, which is a really large variation.
I don’t want to say that this is related to insulin resistance, because you need to do something more to measure insulin resistance. You should use a clamp technique, and this was not done. I am not saying that these differences are necessarily significant, but if they are real, they have implications for what has been said in the literature about the chronic action of insulin on the maternal vessels and on the electrolyte content of the vessels. I think we should be aware of that.

Dr. Doris Campbell: We ought to be careful about extrapolating from the results of glucose tolerance testing done at an isolated time in pregnancy to what might be a longitudinal happening, because pregnant women don’t drink 100 g of glucose with regularity; they eat food, and the endocrine response in pregnancy is such that it keeps plasma glucose in a very tight band. We must be careful about extrapolating from high levels in response to very high, unphysiologic glucose loading.

Dr. Battaglia: I don’t put much credence in the idea that development of any kind of reduction in glucose supply to the pregnant uterus is going to produce growth retardation, because Bill Hay in our department has been producing profound hypoglycemia in pregnant sheep for weeks, and the effect on fetal growth is really minimal—he is getting a 15% reduction in fetal weight, in a species in which you can produce striking growth retardation by other techniques. So I think a limitation of glucose supply alone in large mammals is very unlikely to be a cause of the growth retardation.

Dr. Campbell: I thought it had been shown reasonably conclusively that maternal undernutrition in third-world countries is associated with SGA fetuses.

Dr. Battaglia: We come back to Doris Campbell’s point; with undernutrition you are reducing amino acid intake. I am talking about glucose alone. If you restrict glucose, I doubt whether it is going to produce growth retardation in any large mammal.

Dr. Pardi: How did you select the patients followed longitudinally starting from 20 to 24 weeks?

Dr. Valensise: With Doppler evaluation. These patients came from a group of patients referred to our clinic, and they underwent Doppler only when they were in the first pregnancy or they had a previous pathology in their pregnancy that could be related to uteroplacental insufficiency: previous fetal death, previous intrauterine death, previous growth retardation, previous small baby. Those were the selection criteria.

Dr. Boyd: Would it make any difference at all if you used systolic blood pressure from your recordings rather than diastolic? They seem to be extraordinarily parallel.

Dr. Valensise: The slide that you saw was only a graphic reconstruction. When we use systolic blood pressure, we don’t have the same results—they are much less significant. The diastolic value is much more useful in this sort of evaluation in the absence of clinical hypertension.

Dr. Boyd: So the slide you showed was atypical, where they were very parallel?

Dr. Valensise: Yes, it was just a representation.

Dr. Foumie: Did you try to link the difference between diurnal and nocturnal pressure measurements?

Dr. Valensise: When these machines first appeared in our department, there was great enthusiasm about the possibility of circadian variation, and people were eagerly awaiting the results to see if there might be differences between patients who retained the normal rhythm and those who had lost it, trying to see whether treatment at a certain time of day could be directed toward restoring the normal rhythm. However, in the patients with a confirmed diagnosis of pre-eclampsia or nonproteinuric pre-eclampsia with growth retardation, the incidence of loss of circadian rhythm was very low, somewhere around 20% to 25%.
Dr. Stuart Campbell: You showed maternal endothelial damage. Could you elaborate on that? What causes this endothelial damage, especially as the endothelium is replaced in the spiral arteries by trophoblast? It always seemed to me to be one of the great mysteries as to why the endothelium is replaced by the placenta. There must be a physiologic reason for that.

Dr. Valensise: It is said that what causes the endothelial damage is a multifactorial process that starts with a reduction in the hemodilution and the presence of hemoconcentration that would increase the sheer stress on the endothelium, and the macrophages or neutrophils would deposit part of their content of aggregating molecules, which will lead to problems.

Dr. Stuart Campbell: You found sustained increased blood pressure in your normal IUGR group. Why?

Dr. Valensise: It was not sustained, but it was certainly different from the median values of the control group. In a scatter diagram, these are in the lowest part, nearer the normal than the abnormal, but they are similar to values in patients who have gestational hypertension without proteinuria. I don’t know why. Redman has described normotensive preeclampsia, in which the damage to the implantation is not directed toward the maternal organism but toward the fetus (1, 2). I don’t know whether this is true, and I don’t know why this happens.

Dr. Herrera: I would like to comment on damage to the endothelium in this condition. I don’t know anything about preeclampsia, but it seems to me, at least from the literature, that in this condition there is a large increase in oxidative stress and an increased production of free radicals. These free radicals are taken up by the endothelial cells and maybe could contribute to the damage.

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