Insulin in obstetrics: a main parameter in the management of pregnancy

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Insulin plays a central role in human pregnancy. Maternal insulin sensitivity decreases with advancing gestation in order to provide glucose and possibly other nutrients for feto-placental growth and energy needs. Moreover, alterations of insulin metabolism are clearly involved in the development of gestational diabetes. In recent years, hyperinsulinaemia has been also proposed as a possible pathogenic factor in the development of gestational hypertension and pre-eclampsia; furthermore it has also been postulated that there is an involvement of insulin sensitivity in fetal growth restriction. These intriguing data have stimulated our interest in summarizing the physiopathological mechanisms by which the pancreatic hormone could be involved in obstetrics.

Key words: diabetes/fetal growth/hypertension/insulin/pregnancy

Introduction

Insulin plays a central role in human physiology; the classical effects of insulin include regulation of carbohydrate, lipid and protein metabolism in the liver, muscle and adipose tissue. In addition, insulin also acts on the ovaries, skin, kidney and blood vessels, which all express the classic insulin receptors (Poretsky and Kalin, 1987). The effects of insulin include not only stimulation of glucose transport and inhibition of lipolysis, but also stimulation of DNA and protein synthesis, stimulation of electrolyte transport across the cell membrane, enhancement of steroidogenesis, etc. (Reaven, 1988). Resistance to insulin-stimulated glucose uptake is a quite common phenomenon and is a main factor in the pathogenesis and clinical course of several important human diseases; nowadays, it is generally recognized that insulin resistance is characteristic of patients with either impaired glucose tolerance (IGT) or non-insulin-dependent diabetes mellitus (NIDDM) (Reaven, 1988). On the other hand, hyperinsulinaemia and insulin resistance are common findings in hypertensive individuals (Ferranini et al., 1991). Patients with hypertension and insulin resistance often have elevated serum triglycerides and decreased high-density lipoprotein cholesterol (HDL-C) concentrations. It has been suggested that insulin resistance might be the common aetiological factor causing hyperinsulinaemia, hypertension, hypertriglyceridemia and low serum HDL-C, a cluster of risk factors for coronary artery disease also designated ‘syndrome X’ (Reaven, 1988) or ‘insulin resistance syndrome’ (Ferranini et al., 1991).

Insulin also plays a central role in pregnancy and in several complications of gestation, such as gestational diabetes and hypertension. It therefore seems of great interest to summarize the physiopathological mechanisms by which the pancreatic hormone could be involved in obstetrics.

Insulin and the physiology of pregnancy

Glucose metabolism

Pregnancy has often been characterized as having a diabetogenic effect on normal carbohydrate metabolism, as manifested by hyperglycaemia and hyperinsulinaemia in response to maternal feeding (Cruikshank et al., 1986).
During normal pregnancy, there is a progressive increase in maternal insulin secretory response to glucose and various other stimuli (Spellacy and Goetz, 1963; Bleicher et al., 1964; Cousins et al., 1980); this increase represents an adaptation to cope with the increasing demands of the fetus, necessary for its rapid growth.

Assessment of glucose metabolism during gestation previously consisted only of measurements of fasting glucose and insulin, and the response to oral and intravenous glucose challenges. With the development of more sophisticated techniques, various components of glucose metabolism have been examined in greater detail (Catalano, 1994). Precise estimates of peripheral insulin sensitivity can now be assessed in pregnant women using methods such as the hyperinsulinaemic–euglycaemic glucose clamp (De Fronzo et al., 1979) and the minimal model technique (Pacini and Bergman, 1986). Other techniques allow us to evaluate if resistance to the action of insulin may be due to prereceptor (abnormal ligand or competition), receptor (abnormal structure, affinity or number of receptors), or post-receptor events. In this regard, it has to be considered that the insulin receptor is a heterotetramer glycoprotein consisting of two α-subunits and two β-subunits. The α-subunits are located extracellularly and contain the insulin-binding domain, whereas the β-subunits span the cell membrane and project intracellularly. Insulin binds to the α-subunits transmitting a signal to the β-subunits, which in turn activate protein tyrosine kinase, an enzyme present on its cytoplasmic domain; the resulting phosphorylation of the tyrosine residues is an obligatory step of insulin action (Goldfine, 1987; Kahn and White, 1988). Each of these stages, as well as subsequent ones, could be responsible for a state of insulin resistance.

Little information is available concerning glucose metabolism in early gestation; Spellacy et al. (1965b) did not report significant differences in fasting glucose and insulin concentrations in women in early pregnancy when compared to those in non-gravid subjects. Catalano et al. (1992), by analysing non-obese healthy women, showed a slight (but not significant) decrease in fasting glucose and insulin concentrations from the time before conception through 12–14 weeks gestation. Similarly divergent results were found by these authors in the analysis of glucose-stimulated insulin concentrations. Spellacy et al. (1965b) showed no significant increase in total insulin response to an intravenous glucose tolerance test (IVGTT) at 13–15 weeks gestation when compared to results in the same subjects examined postpartum. Conversely, Catalano et al. (1991), in a prospective longitudinal IVGTT study in non-obese women, showed a 120% increase in first-phase insulin response and a 50% increase in second-phase insulin response by 12–14 weeks gestation, thus suggesting an early appearance of insulin resistance during pregnancy.

Other authors have made hypotheses about insulin resistance in early pregnancy: Kalkhoff et al. (1979) suggested that first-trimester gestation is characterized by increased insulin sensitivity, on the basis of improved IVGTT in women in early pregnancy compared with non-gravid controls. Coustan and Felig (1988) postulated that the decreased insulin requirement in early gestation seen in insulin-dependent diabetic women is a function of decreased glucose availability. Knoop et al. (1981) attributed increased maternal fat storage in early gestation to an increased secretion of insulin associated with increased caloric intake. Yen (1973), on the basis of a longitudinal assessment of insulin–glucose relationships during normal pregnancy and postpartum, suggested an increased sensitivity to exogenous insulin during the first trimester of pregnancy.

Nevertheless, the gold-standard method for the evaluation of insulin sensitivity could be considered to be the hyperinsulinaemic–euglycaemic clamp technique. This technique uses the rate of glucose infused to maintain plasma glucose constant in the face of hyperinsulinaemia as the basis for estimating insulin resistance (Coates et al., 1995), and is thus able to evaluate peripheral insulin sensitivity without involving endogenous insulin secretion. The first (and to our knowledge unique) application of this technique in estimating changes in peripheral insulin sensitivity in women in early pregnancy was reported by Catalano et al. (1992), who found a significant (~40%) decrease in insulin sensitivity from the time before conception through 12–14 weeks gestation.

There is generally agreement about the reduction of insulin-mediated glucose uptake and the presence of hyperinsulinaemia during late pregnancy. It has been shown since the early 1960s (Spellacy and Goetz, 1963; Spellacy et al., 1965a) that there is a significant and progressive increase in insulin response to an IVGTT in women in mid- and late gestation when compared with results for the same subjects postpartum. Ryan et al. (1985), by analysing uncomplicated human pregnancies with the euglycaemic clamp method, found a difference in step-down in glucose infusion rate (an index of insulin sensitivity) between non-pregnant and pregnant women. Buchanan et al. (1990), by using minimal model analysis, revealed that lean and moderately obese women during the third trimester of pregnancy had insulin sensitivity that was reduced by approximately two-thirds as compared with a group of non-pregnant women of similar age and relative weight. Furthermore, in the face of this marked insulin resistance, first- and second-phase pancreatic β-cell...
responses to glucose were increased approximately threefold in the normal pregnant women as compared with non-pregnant subjects. The fact that insulin sensitivity in the pregnant group was reduced to one-third of non-pregnant controls, whereas insulin responses were increased threefold, seems to indicate that the alterations in insulin action and β-cell function are not simply qualitatively reciprocal, but also quantitatively reciprocal in nature. In keeping with these data are those of Catalano et al. (1992), who found a 56% decrease in insulin sensitivity by 34–36 weeks gestation in normal pregnant women. Other data in the literature show a gradual increase of insulin and c-peptide response to the oral glucose tolerance test (OGTT) during the course of pregnancy (Agardh et al., 1996), thus suggesting a progressively increased insulin secretion. The morphological background for these enhanced plasma insulin concentrations in pregnancy is a marked β-cell hypertrophy and hyperplasia (Van Assche, 1974; Van Assche et al., 1978).

The reciprocal appearance of hyperinsulinaemia and insulin resistance during pregnancy does not reveal if enhanced β-cell function is compensatory to insulin resistance or vice versa. In order to clarify the mechanisms by which insulin resistance develops during gestation, a great deal of attention has been given to the major components of the insulin action sequence: the receptor, the receptor tyrosine kinase activity, and the glucose transport system.

**Mechanisms of insulin resistance in pregnancy**

Insulin receptor binding to circulating cells from pregnant subjects has been found, in most cases, not to differ from normal values (Tsibris et al., 1980; Gratacos et al., 1981; Moore et al., 1981; Toyoda, 1982), although there are also reports of an increase (Andersen, 1990; Dwenger et al., 1982; Puavilai et al., 1982) or decrease (Beck-Nielsen et al., 1979). However, blood cells do not represent a classic insulin target tissue, and their concentration of insulin receptor often does not correlate with receptor concentrations in adipocytes from the same individual (Pedersen et al., 1982). More recently, other study groups have investigated the cellular mechanisms underlying insulin resistance during pregnancy by employing a classic insulin target tissue, isolated adipocytes. Using this model, the insulin-receptor binding in pregnant women at term has been reported to be lower (Pagano et al., 1980; Hjollund et al., 1986; Ciaraldi et al., 1994), or similar (Andersen and Kuhl, 1988; Damm et al., 1993) to the binding in healthy non-pregnant women. The reasons for such conflicting results are not clear, although if they might be explained by differences in biopsy sites and dietary habits in the investigated women (Bolinder et al., 1983; Graig et al., 1987; Kuhl, 1991).

On the other hand, it seems that insulin resistance in pregnancy occurs in the presence of normal insulin receptor kinase activity (Damm et al., 1993; Ciaraldi et al., 1994). Bruce et al. (1992) seemed to confirm that pregnancy-induced insulin resistance is not caused by a tyrosine kinase defect in adipose tissue. Conflicting reports, have arisen, however, from animal studies in which tyrosine kinase activity was found to be either normal (Camps et al., 1990) or decreased (Martinez et al., 1989; Saad et al., 1997).

From the bulk of the above discussed data from the literature, it could be postulated that the primary cellular pathogenic mechanism responsible for insulin resistance in normal pregnancy might be located distal to the activation of the insulin receptor tyrosine kinase. Another possible hypothesis to explain the reduced insulin sensitivity in pregnancy might consist of alterations in the insulin receptor microenvironment, which could modulate the insulin receptor activity. Camps et al. (1990), by analysing skeletal muscle of pregnant rats, found an inhibitory factor of insulin binding, which had previously also been obtained in sarcolemmal membrane fractions from rat skeletal muscle (Whitson et al., 1988), thus suggesting that this factor might play a regulatory role in insulin receptor function in vivo.

An anti-insulin effect has been also suggested for pregnancy hormones. The strong correlation between progression of pregnancy and increasing concentrations of human placental lactogen (HPL), oestrogens (E1, E2, E3), progesterone and cortisol first suggested a possible causal relationship between these rising hormone concentrations and endogenous insulin concentrations (Cousins, 1991). These initial observations suggesting hormone induction of impaired insulin-mediated glucose disposal were followed by studies in which administration of gestational hormones produced increased insulin secretion and insulin/glucose ratios (Kalkhoff et al., 1969; Burke and Roulet, 1970; Costrini and Kalkhoff, 1971), and enhanced islet concentration of insulin (Costrini and Kalkhoff, 1971). The cellular mechanisms whereby gestational hormones might induce insulin resistance were examined by Ryan and Enns (1988), who found that HPL, prolactin, progesterone and cortisol, at concentrations similar to those found in the third trimester of normal pregnant women, are capable of inducing insulin resistance in an adipocyte culture system, by acting at the level of insulin/receptor binding and glucose transport.

In summarizing data from the literature, we could conclude that during pregnancy a condition of insulin resis-
Insulin and gestational diabetes

Gestational diabetes mellitus (GDM), defined as glucose intolerance that has its onset or first recognition during pregnancy (Clark et al., 1997; Kautzky-Willer et al., 1997), occurs in 2–5% of pregnancies (Buchanan and Catalano, 1995). Since its first description by O’ Sullivan and Mahan (1964) in the early 1960s, GDM has been one of the most controversial syndromes in the field of diabetes. The importance of GDM can also be highlighted by the very high and cumulative ‘conversion rate’ of patients previously diagnosed with GDM to NIDDM, ranging from 6.8 to 92% for combined impaired glucose tolerance and overt diabetes, and from 2.9 to 50% for diabetes alone (Bevier et al., 1995).

Many studies have been performed in order to assess the relative contribution of decreased insulin sensitivity and impaired β-cell secretion in the pathogenesis of GDM. Fisher et al. (1980) reported that insulin sensitivity, as estimated by a glucose infusion test, was significantly greater in 15 non-obese women with gestational diabetes than it was in a control group. Ryan et al. (1985), by using the hyperinsulinaemic–euglycaemic clamp, reported that women with GDM had decreased insulin-stimulated glucose uptake compared with women in a non-diabetic pregnant control group. Similar results were also obtained by Catalano et al. (1993); the same authors showed that there was a significant decrease in insulin sensitivity with advancing gestation in both pregnant women with normal glucose tolerance and those with GDM. The decrease in insulin sensitivity was progressive in normal pregnant patients. However, women who developed GDM, and who were starting from lower insulin sensitivity before pregnancy when compared to control subjects, did not show variations in the insulin sensitivity index through the first trimester, but the insulin resistance progressively increased until the term of pregnancy.

In contrast with these data, Buchanan et al. (1990), by using an IVGTT, showed that during the late phase of pregnancy, GDM was not accompanied by insulin resistance beyond that accounted for by the effect of gestation per se. However, Persson et al. (1997), with a similar study method, suggested that GDM patients might have a selected defect in insulin action compared with normal pregnant patients. In accordance with these data are those by Bowes et al. (1996) in a group of obese GDM patients. Such discrepancies in the evaluation of insulin sensitivity in GDM patients can probably be partly explained by the difficulties in matching GDM and control patients for weight, weight gain and body mass index. In an attempt to analyse the glucose metabolism of this pathology better, Kautzky-Willer et al. (1997) recently analysed, with an IVGTT, the insulin sensitivity of a group of lean subjects with GDM, showing that these patients feature more pronounced insulin resistance during pregnancy than pregnant subjects with normal glucose tolerance, and this does not completely abate after delivery.

Mechanisms of insulin resistance in GDM

The mechanisms underlying insulin resistance in GDM are still not fully understood and only a few studies have been reported that address this issue (Buchanan and Catalano, 1995). Compared with pregnant control women, insulin receptor binding to erythrocytes (Cheney et al., 1985; Andersen and Kuhl, 1987; Skouby et al., 1987), monocytes (Neufeld et al., 1984; Pedersen et al., 1986; Andersen and Kuhl, 1987) and placenta (Duran-Garcia et al., 1979) has been variably reported to be normal, decreased, or increased in patients with GDM. Conflicting reports exist also about the insulin-receptor relationship at the adipocyte level (Pagano et al., 1980; Hjollund et al., 1986; Andersen...
and Kuhl, 1988; Bruce et al., 1992). Damm et al. in 1993 showed that the insulin resistance found in a gestational diabetic pregnancy is not likely to be caused by a defective insulin receptor tyrosine kinase, whereas decreased insulin receptor binding might have some pathogenic importance in this pregnancy complication; however, these authors were not able to disclose whether the decreased insulin binding was due to a down-regulation of the receptor number caused by the hyperinsulinaemia or was a primary defect. Thus, most if not all cellular insulin resistance could be attributable to defects that lie distal to receptor binding and tyrosine kinase activity in the insulin action pathway. Garvey et al. (1993) demonstrated a mean 50% reduction of insulin-stimulated glucose transport into omental adipocytes removed from women during caesarean section, compared with non-diabetic women; this reduction could be due to a profound depletion in the GLUT4 (a glucose transporter protein) content in adipocytes, but this was found only in about one-half of the entire group of GDM patients. In any case, all studied subjects were found to exhibit an abnormality in GLUT4 subcellular distribution, suggesting that abnormalities in cellular traffic or targeting relegate GLUT4 to a membrane compartment from which insulin cannot recruit transporters to the cell surface, and this could thus be responsible for the insulin resistance in GDM.

In the pathogenesis of GDM, the β-cells also play a key role; in fact, during normal pregnancy, the marked reduction of insulin sensitivity could be compensated by a reciprocal increase in β-cell secretion. In contrast, the β-cell adaptation to insulin resistance is impaired in women with GDM; indeed several investigators have demonstrated that women who developed gestational diabetes in late pregnancy displayed a first-phase insulin response to IVGTT that was significantly reduced when compared with that of pregnant women with normal glucose tolerance (Yen et al., 1971; Fisher et al., 1980; Buchanan et al., 1990; Catalano et al., 1993). The IVGTT can be generally analysed as a first- and a second-phase response; a decrease in first-phase insulin response (usually the first 10 min) is one of the earliest signs of β-cell dysfunction and is associated with a significant deterioration of glucose tolerance (Bergman et al., 1985).

From the bulk of the above described data, it could be argued that glucose intolerance in gestational diabetes compared to normal pregnancy may be due to both reduced insulin sensitivity and an impaired ability to increase insulin secretion in response to glucose (Bowes et al., 1996; Persson et al., 1997). On the other hand, Buchanan et al. (1990) suggested that there is clearly heterogeneity of β-cell function in women with GDM and that a β-cell dysfunction rather than abnormally increased insulin resistance might be the predominant abnormality in women with mild GDM during the third trimester.

Theoretically, insulin clearance could also be involved in the pathogenesis of GDM; however, to our knowledge, the only report analysing liver insulin metabolism in gestational diabetes failed to find any difference in hepatic insulin extraction between the pregnant women with GDM and those with normal glucose tolerance, thus arguing against any potential effect of hepatic insulin clearance on the alteration of glucose tolerance during gestation (Kautzy-Willer et al., 1997).

An issue to be addressed in the evaluation of insulin involvement in GDM is represented by the fact that there is a wide variability in the insulin response to an oral glucose tolerance test (OGTT) in women developing carbohydrate intolerance during pregnancy (Caruso et al., 1994; Di Simone et al., 1996), ranging from a reduction of pancreatic islet function to a normal or exaggerated secretory pattern of insulin. These differences may have some implications in terms of therapeutic approach as well as fetal and maternal pregnancy outcome.

Polycystic ovary syndrome and gestational diabetes

Insulin might be considered a risk factor for the development of gestational diabetes in patients with polycystic ovary syndrome (PCOS) (Lanzone et al., 1995, 1996); indeed, we have previously shown that women with PCOS are more likely to exhibit impaired carbohydrate metabolism during pregnancy (Lanzone et al., 1995). The prevalence of impaired gestational glucose tolerance or frank diabetes in PCOS is ~46% (Lanzone et al., 1996), significantly higher than in the general population. Moreover, in our series, by analysing PCOS women accordingly to their insulin secretion, we found that only hyperinsulinaemic PCOS pregnant patients developed impaired carbohydrate metabolism. In order to elucidate the mechanisms of metabolic adaptation of PCOS women during pregnancy, we recently longitudinally studied a group of PCOS patients during the three trimesters of gestation (Paradisi et al., 1998). Our data showed that, already in the first trimester of pregnancy, PCOS patients who subsequently developed gestational diabetes had significant differences compared with unaffected PCOS subjects: they showed higher glucose and insulin plasma concentrations after an OGTT and a reduced insulin sensitivity as evaluated by the euglycaemic–hyperinsulinaemic clamp. These features in part resemble those shown by Catalano et al. (1993) in women who developed GDM during the course of pregnancy, and
allow us to postulate the possibility of an early identification of PCOS subjects who subsequently could develop GDM.

Furthermore, among PCOS pregnant women, those with normal glucose tolerance and those with GDM exhibited a similar absolute insulin increase to OGTT during the course of gestation, thus suggesting that insulin secretion by the pancreas is not reduced in PCOS patients with gestational diabetes, even if it was not able to compensate for the greater impairment of insulin sensitivity. This is also suggested by the higher insulin response to OGTT found in gestational diabetic PCOS patients as compared to a group of patients with GDM, in spite of a similar degree of insulin resistance during the third trimester (Paradisi et al., 1998). Thus, it could be argued that PCOS women with GDM may represent a specific subgroup, from a physiopathological point of view.

The presence of an association between PCOS and GDM has been recently confirmed by Holte et al. (1998); these authors showed an exceptionally high prevalence of polycystic ovaries (41%) in a group of women with previous gestational diabetes, who were mainly characterized by exaggerated insulin resistance at the peripheral level rather than by an impairment of β-cell function. Furthermore, the women with PCOS and GDM had a higher prevalence of pregnancy-induced hypertension than the women with GDM but with normal ovaries. On the other hand, an increased prevalence of labile blood pressure has been found in PCOS, which may indicate a pre-hypertensive state (Holte et al., 1996). The observation that insulin resistance and hyperinsulinaemia are repeatedly found in association with hypertension out of (Ferranini et al., 1987; Pollare et al., 1990) as well as during pregnancy (Sowers et al., 1995a; Laivuori et al., 1996), coupled with the presence of a high prevalence of hyperinsulinaemia in PCOS (~70% of obese but also 20–40% of lean PCOS subjects (Lanzoni et al., 1990; Ciampelli and Lanzoni, 1998)), could lead to the hypothesis that hypertensive complications in pregnancy may be common in PCOS patients, probably related to the insulinaemic patterns.

The importance of the above discussed data is suggested by the high prevalence of PCOS, which affects up to 10% of women of reproductive age (Franks, 1995), and the rapid progress in the assisted reproductive techniques which permit pregnancies in such anovulatory patients.

Insulin and gestational hypertension

In the past few years, the possible effects of insulin on the circulation have received a great deal of attention; indeed many reports (Fournier et al., 1986; Ferranini et al., 1987) have suggested an association between hyperinsulinaemia and hypertension. Insulin and insulin-like growth factors (IGF) are mitogens capable of stimulating smooth muscle proliferation and vascular hypertrophy (Pfeifle et al., 1981; King et al., 1985), thus narrowing of the lumen of resistance vessels, ultimately leading to the development of hypertension. Furthermore, insulin has been documented to stimulate the activity of the sodium–proton exchanger in skeletal muscle and adipocytes (Mukherjee and Mukherjee, 1981; Putnam, 1985), with intracellular calcium accumulation, which would be expected to enhance the sensitivity of the vascular smooth muscle to the pressor effects of norepinephrine and angiotensin (Hersmeyer, 1987; Dominiczak and Bohr, 1989). On the other hand, the increased sodium–proton exchange could also lead to intracellular alkalosis (Boron, 1986), which in turn could be responsible for a stimulation of protein synthesis and cell proliferation (Lever, 1986). Moreover, lipid alterations induced by hyperinsulinaemia (Reaven, 1988; Oppenheimer et al., 1989; Ferranini et al., 1991; Weidman et al., 1993) may promote atherosclerosis, with arterial stiffening and narrowing. These mechanisms could be also operative for uteroplacental circulation, so that a relation between insulin and hypertension during pregnancy could be postulated. Bauman et al. in 1988 were the first to suggest the presence of such an association during gestation; these authors found hyperinsulinaemia with normal glucose tolerance in a group of pregnant women with high blood pressure as compared with normotensive pregnant women. However, the comparison was not controlled for obesity, nor was it specified whether the hypertensive women had chronic essential hypertension, gestational hypertension, or pre-eclampsia.

Subsequently, Kaaja et al. (1995) demonstrated more clearly that women with pregnancy-induced hypertension (PIH) are more hyperinsulinaemic than normotensive control subjects; furthermore they showed that the hypertensive pregnant women exhibited high triglyceride and insulin concentrations and low HDL-C concentrations, findings that resemble key characteristics of the ‘insulin resistance syndrome’. Using a cohort study design, other reports have highlighted a positive relationship between hyperinsulinaemia in the second trimester and development of pre-eclampsia (Sowers et al., 1995b) or PIH (Cioffi et al., 1995; Hamasaki et al., 1996) during the third trimester. However, in a further evaluation of their data, Cioffi et al. (1997) failed to find differences in insulin concentrations between normotensive pregnant subjects and those with PIH after controlling for confounding variables including body mass index, race and age, thus suggesting that hyperinsulinaemia seem not to be a major determinant of blood pressure during pregnancy. Partially concurring with these data are those of
Bartha and Comino-Delgado (1997), who found that normal insulin activity occurs in pre-eclampsia. By contrast, Martinez Abundis et al. (1996) showed that postload plasma insulin concentrations were nearly fourfold higher in a group of pre-eclamptic women as compared with control pregnant subjects.

The presence of a causal link between pre-eclampsia and insulin resistance seems to be confirmed by the persistence of these features after pregnancy; indeed Fuh et al. (1995), by analysing women 2 months after delivery, found that women who developed pre-eclampsia were relatively insulin resistant and hyperinsulinaemic when compared to those who had an uncomplicated pregnancy. Similarly, Laivuori et al. (1996) compared carbohydrate metabolism many years later in women who had had pre-eclampsia to those who had not, and showed that previously pre-eclamptic women were characterized by significantly elevated insulin concentrations but normoglycaemia 17 years after such pre-eclamptic pregnancies. Finally, it seems that, independently of the following development of gestational hypertension, hyperinsulinaemic pregnant women show higher systolic and diastolic blood pressure values as compared to normoinsulinaemic pregnant subjects (Hamasaki et al., 1996).

Few studies are available concerning the possible cellular mechanisms of insulin resistance in pregnancy-induced hypertension. Sowers et al. (1995a) examined erythrocyte insulin and IGF-I receptor tyrosine kinase activity in nulliparous African American women developing hypertension in pregnancy and in their gestational controls; they did not find differences between the studied groups with regard to insulin binding (number and affinity of insulin receptors). However, pre-eclamptic subjects showed a significant increase in insulin-stimulated tyrosine kinase activity compared with controls, thus suggesting that insulin resistance in this disorder may be at the post-kinase step, perhaps reflecting altered mobilization of glucose transporters. Indeed, an increased kinase activity seems to be related to a post-receptor abnormality (Agino et al., 1994). On the other hand, Valensise et al. (1996) reported decreased insulin binding at the placental level in hyperinsulinaemic women with gestational hypertension as compared to normoinsulinaemic ones.

Another issue to be addressed regards the data of Solomon et al. (1994), who showed that an abnormal glucose screening test was a significant predictor of development of gestational hypertension independent of obesity. Thus, GDM could be considered a risk factor for gestational hypertension; however, in our previous reports we identified a subset of the GDM population who present increased risk as compared to the general GDM population (Caruso et al., 1994; Di Simone et al., 1996). Indeed, insulin secretory patterns are heterogeneously represented in GDM patients, as discussed in a previous section, and hyperinsulinaemic GDM patients exhibit a higher prevalence (~35–40%) of blood pressure disturbances as compared to normo- and hypo-insulinaemic patients (~5–10%) (Caruso et al., 1994; Di Simone et al., 1996).

In a further evaluation of the haemodynamic role of insulin during pregnancy, we have recently analysed the possible relationship between the insulin response to a glucose load and utero-placental resistances to blood flow, as evaluated by Colour Doppler, in third trimester pregnancies complicated by carbohydrate intolerance (Caruso et al., 1998a); our data showed that women with exaggerated insulin secretory patterns after glucose load had higher uterine vascular resistance indices when compared to control subjects, thus suggesting a possible involvement of insulin as a regulating factor in utero-placental circulation.

### Insulin and Fetal Growth

The endocrine regulation of fetal growth in late gestation is determined by hormones that influence the partitioning of nutrients between mother, placenta and fetus, as well as those that affect fetal nutrient uptake and promote fetal somatogenesis (Gluckman, 1995). Insulin and IGF-I, acting through their highly homologous receptors localized predominantly on the microvillous membrane of the syncytiotrophoblast (Wolf and Desoye, 1993) are thought to play a key role in the growth and development of the feto-placental unit (Whitsett and Lessard, 1978; Desoye et al., 1992; Reece et al., 1994).

Correlations between insulin/IGF concentrations (evaluated by cord blood samples) and neonatal size at birth are well established (Lassarre et al., 1991; Baker et al., 1993; Gluckman, 1995); however, few data are available about the possible involvement of maternal factors on fetal growth. Several reports have highlighted the importance of the mother’s anthropometric characteristics and carbohydrate metabolism; in particular pre-gravid weight, weight gain during pregnancy and maternal glucose concentrations in response to glucose load showed positive correlations with neonatal weight at birth (Breschi et al., 1993; Abrams and Selvin, 1995; Neggers et al., 1995).

Other authors have also postulated a key role for insulin and related growth factors. Mirlesse et al. (1993) suggested that maternal IGF-I might play a particular role in determining nutrient supply to the fetus, since in late gestation maternal IGF-I concentrations were found to be reduced in pregnancies complicated by intrauterine growth retardation (UGR). Breschi et al. in 1993 described the presence of an inverse relationship between insulin response to
glucose load and infant birthweight in a group of non-diabetic, normotensive, lean pregnant women.

Starting from these data, Catalano et al. (1995) evaluated in a prospective analysis the possible influence of insulin sensitivity on placental and neonatal birthweight, and showed the presence of a significant inverse correlation between the above specified parameters; they concluded that maternal insulin sensitivity, particularly in late gestation, is crucial for regulation of nutrient availability to the fetus and the placenta. These data were only partly confirmed in a subsequent study by Bernstein et al. (1997); in fact, these authors showed that, even though a relationship between maternal insulin sensitivity and birthweight percentile was found, in a stepwise regression analysis maternal insulin-mediated glucose availability did not provide an independent contribution to either newborn ponderal index or birthweight percentile.

It has been also observed that in women with fetal growth retardation (IUGR), glucose and insulin plasma concentrations after oral glucose load are lower than in women with normal pregnancies (Khouzami et al., 1981; Sokol et al., 1982; Piper et al., 1996), thus suggesting that maternal carbohydrate metabolism might be involved in the pathogenesis of IUGR.

In order to verify this hypothesis, we recently analysed insulin-stimulated glucose uptake in a group of pregnant patients affected by IUGR, and showed that IUGR pregnancies were characterized by a relatively higher maternal insulin sensitivity (by 22%) and lower plasma insulin and glucose concentrations after OGTT when compared to patients with normal fetal growth (Caruso et al., 1998b). It is likely that the greater peripheral insulin sensitivity of women with IUGR can, on the one hand, induce less necessity for insulin secretion to maintain an euglycaemic state and, on the other hand, lead to a more efficient consumption of glucose, with lower glycaemic concentrations compared to women with normal fetal growth. It could be speculated that the greater insulin sensitivity found in such complicated pregnancies can induce a maternal competition for the metabolic substrates, with a decreased glucose shunt to the placenta–fetal compartment, resulting in reduced fetal growth. Starting from current knowledge, future studies will be able to clarify the complex mechanisms which regulate and determine fetal growth.

Conclusions

Insulin is a ubiquitous hormone, with effects on the ovaries, skin, kidney, blood vessels and other organs; on the other hand, this pancreatic hormone also seems to play a central role in obstetrics. It is well established that normal pregnancy is associated with insulin resistance; indeed, pregnant women without hyperglycaemia have higher insulin concentrations after glucose administration, indicating that a greater than normal amount of insulin is necessary to achieve euglycaemia. On the other hand, insulin disturbances are involved in the pathogenesis of gestational diabetes, and a role for insulin has recently been suggested also in the pathogenesis of gestational hypertension, as well as in the regulation of fetal growth (see Figure 1).

However, despite the rapid advances in our knowledge on the obstetric involvement of insulin, there are still many open questions. For example, what could be the role of factors other than gestational hormones in the development of insulin resistance during pregnancy? What could be the post-binding defects leading to an abnormal function of the insulin receptor during gestation? What about insulin and fetal growth? Is the fetus less insulin resistant than its mother? Are the children born to mothers with gestational diabetes heavier and labile in blood glucose due to higher insulin sensitivity?

On the other hand, nowadays new research frontiers seem to appear; indeed it has been shown that the acute haemodynamic role of insulin could be mediated by the endothelial-derived relaxing factor (EDRF), and also of note is nitric oxide (Steinberg et al., 1994). Considering that altered nitric oxide concentrations have been reported in amniotic fluid of IUGR fetuses (Di Iorio et al., 1997) and that nitric oxide donors can improve utero-placental circulation (Giles et al., 1992), the new role of insulin appears very intriguing.

In any case, from the bulk of the above summarized data, it seems that insulin should be considered to be a main factor in the management of pregnancy.
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