INSULIN RESISTANCE IN PREGNANCY: IMPLICATIONS FOR GESTATIONAL DIABETES

A.W. BELL, J.A. PETTERSON and R.A. EHRHARDT

Summary

The major thesis of this paper is that gestational diabetes (GDM) represents an extreme in the normal distribution of altered metabolic responses to insulin during late pregnancy. The macrosomia and increased fatness of infants born to GDM patients is consistent with predictable effects of maternal hyperglycaemia on placental glucose transfer, fetal hyperglycaemia and hyperinsulinaemia, and fetal tissue metabolism. Pregnancy-induced metabolic adaptations in maternal liver and peripheral tissues are, to a large extent, mediated by developing insulin resistance which has been characterised in vivo in humans and other species by application of the hyperinsulinaemic, euglycaemic clamp technique. Reductions in insulin sensitivity of whole-body glucose utilisation, and responsiveness of the antilipolytic effect of insulin are, to some extent, consistent with more specifc in vitro observations of altered insulin binding and/or postreceptor responses to insulin in skeletal muscle and adipose tissue. Limited evidence suggests that some of these altered cellular responses to insulin are exaggerated in cases of GDM compared to normal pregnancies. It is highy likely that maternal insulin resistance is effected through the homeorhetic actions of placental and other hormones, including placental lactogen and oestrogens. Clear evidence for the efficacy, relative importance, and modes of action of these hormones remains to be obtained.

I. INTRODUCTION

For the purpose of this paper, human gestational diabetes mellitus (GDM) is defined as diabetes diagnosed for the first time during pregnancy which then resolves postpartum. This complex and heterogeneous syndrome occurs, on average, in about 3% of pregnancies in western societies, most commonly in obese women and those over 30 years old (Weiss 1988). It is associated with significantly increased incidence of perinatal mortality and morbidity (Weiss et al. 1984), and often, with the development of overt diabetes in the mother in later life (O'Sullivan 1984). There is also increasing evidence that the offspring of gestationally diabetic women have increased predisposition to diabetes as adults, raising thc possibility that GDM is perpetuated from generation to generation (Aerts et al. 1990).

The aetiology and patho-physiologic basis of GDM are diverse and mechanistically obscure. However, all well-described manifestations of the syndrome are characterised by maternal insulin resistance, possibly associated with relatively inadequate pancreatic insulin secretion (Kuhl and Andersen 1988). Progressive insulin resistance is typical of normal pregnancy in humans and other mammals, and is presumably an adaptation to ensure that glucose requirements of the conceptus are met. even when maternal glucose supply is compromised. This results in the phenomenon known as the 'glucose sparing effect of pregnancy'. Although it has been suggested that some women predisposed to GDM may be genetically distinct (Ober et al. 1989), we believe it is more likely that most cases represent one end of a normal distribution of pregnancy-induced alterations in insulin-dependent glucose disposal. Therefore, this review will focus on possible mechanisms for the development of insulin resistance in maternal tissues during late pregnancy,

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Department of Animal Science, Cornell University, Ithaca New York 14853, USA

with reference to evidence from in vivo studies on sheep and laboratory animals, and to clinical studies on humans where appropriate.

II. REGULATION OF CONCEPTUS GLUCOSE SUPPLY AND METABOLISM

(a) Glucose supply

The importance of glucose as a substrate for conceptus metabolism and fetal growth is well documented (Battaglia and Meschia 1988; Bell 1993). In well-fed mothers, fetal and placental glucose requirements are met entirely by placental transport from the maternal bloodstream, which in monotocous sheep accounts for 30-50% of the animal's total glucose supply in late pregnancy (Hay et al. 1983; Leury et al. 1990). Placental glucose transport is achieved by facilitated diffusion and is therefore strongly influenced by the gradient in glucose concentration between maternal and fetal arterial bloodstreams (Simmons et al. 1979).

Recent evidence suggests that in humans (Hauguel-de Mouzon et al. 1994), sheep (Ehrhardt et al. 1994), rats (Zhou and Bondy 1993) and probably, other species, the functionally predominant glucose transport protein in the placenta is GLUT-1. The abundance and affinity (K_m) of this isoform are such that saturation kinetics for glucose transport do not readily occur under normal conditions, consistent with the close correlations between maternal glycaemia, placental glucose uptake and transfer, and fetal glycaemia observed in vivo (Hay et al. 1990). During more extreme maternal hyperglycaemia, such as may occur in uncontrolled GDM, the placental glucose transport system may be saturated such that fetal glycaemia continues to increase without further increase in net placental glucose transfer (Simmons et al. 1979; Crandell et al. 1983).

Regulation of placental glucose transport, other than by factors affecting the maternal-fetal concentration gradient, is poorly understood. Abundance and activity of the GLUT-1 isoform in other tissues are relatively unresponsive to insulin, consistent with the lack of effect of maternal insulin on placental glucose transport in vivo (Hay et al. 1984; Rankin et al. 1986). However, mRNA abundance for GLUT-1 in cultured human trophoblast was markedly increased in cells deprived of glucose (Hauguel-de Mouzon et al. 1994), which suggests that gene expression of this important transport protein may be nutritionally regulated in vivo. On the other hand, placental GLUT-1 protein abundance was unaltered in genetically diabetic mice with many symptoms of GDM during late pregnancy, suggesting that placental GLUT-1 is not down-regulated by maternal hyperglycaemia (Devaskar et al. 1994).

(b) Fetal glucose metabolism

The association between plasma concentrations of glucose and insulin in the well-oxygenated, late-gestation sheep fetus is well established (Bassett and Fletcher 1982). The insulin secretory capacity of the fetal pancreas to respond to glucose increases developmentally and by late gestation, fetal insulin is a potent regulator of fetal glucose disposal (Hay 1995). This is important because maternal insulin cannot cross the placenta (Alexander et al. 1972). Thus, in women suffering from GDM, maternal hyperglycaemia and its direct consequence, fetal hyperglycaemia, are associated with persistent fetal hyperinsulinaemia which is regarded as a hallmark of the fetopathy of the condition (Weiss 1988).

The role of insulin in regulation of fetal metabolism and growth has been reviewed elsewhere (Gluckman 1986; Fowden 1989). Insulin is clearly required for normal somatic growth and development during prenatal life, as demonstrated by the severe growth retardation caused by natural or experimental ablation of the fetal pancreas (Fowden 1989). On the other hand, chronic fetal hyperinsulinism has been long associated with fetal macrosomia and increased body fatness (Pedersen 1975). We were able to produce this outcome in newborn lambs by infusing them in utero with glucose sufficient to double fetal glycemia and insulinaemia for 30d before term (Stevens et al. 1990). Other studies, in which physiological hyperinsulinaemia was achieved by

prolonged infusions of insulin alone, had smaller or no effects on fetal growth (Milley 1986; Fowden et al. 1989), probably because of the concomitant chronic hypoglycaemia.

Increased fat deposition in the hyperglycaemic, hyperinsulinaemic fetus almost certainly occurs via stimulation of de novo synthesis of fatty acids from glucose in adipose tissue (Vernon et al. 1981b). The degree to which macrosomia occurs in other soft tissues is less well established. However, short-term metabolic studies indicate that increased fetal glucose availability, with or without hyperinsulinaemia, can decrease fetal oxidation of amino acids (Liechty et al. 1992, 1993) and potentially, enhance efficiency of protein deposition.

III. MATERNAL METABOLIC ADAPTATIONS AND INSULIN RESISTANCE IN LATE PREGNANCY

(a) Metabolic adaptations

The principal objective of the manifold adaptations in maternal metabolism during late pregnancy is to sustain the glucose supply of the conceptus, especially when maternal nutrition is suboptimal. In sheep, these adaptations include increased hepatic gluconeogenesis (Steel and Leng 1973; Wilson et al. 1983), reduced glucose utilisation in peripheral tissues (Annison 1990), reduced lipogenesis and increased fatty acid mobilisation in adipose tissue (Vernon et al. 1981a; Petterson et al. 1994), and various, less well-described changes in amino acid metabolism in liver and peripheral tissues (see Bell 1995). Their success is testified by the degree to which fetal growth, expressed as birth weight, is buffered against effects of maternal food shortage, such as during the Dutch famine in World War II (Smith 1947) or in controlled experiments on animals (Robinson 1977).

In almost every case, the metabolic processes involved are strongly influenced by insulin and therefore, susceptible to alterations in pancreatic secretion, receptor binding, postreceptor signal transduction or downstream metabolic effects of this hormone. The rest of this section deals with mechanisms of insulin resistance in maternal tissues during normal pregnancy and GDM, assuming that these are primary mediators of the metabolic adaptations outlined above.

(b) Insulin resistance

(i) Normal pregnancy Present understanding of in vivo mechanisms for the development of insulin resistance during pregnancy has been advanced by application of the hyperinsulinaemic euglycaemic (glucose) clamp technique in women (Ryan et al. 1985; Stanley et al. 1991), sheep (Hay et al. 1988; Petterson et al. 1993) and laboratory animals (Leturque et al. 1984; Hauguel et al. 1987). The more recently developed minimal model has also been used to conconcurrently define effects of human pregnancy on whole-body insulin sensitivity and β-cell responsiveness to glucose in vivo (Buchanan et al. 1990b).

Because only one or two insulin doses were used, glucose clamp studies on women (Ryan et al. 1985; Stanley et al. 1991) were unable to distinguish whether the insulin resistance of pregnancy was due to a reduction in sensitivity, responsiveness or both of insulin-dependent glucose metabolic responses, as defined in the conceptual model of Kahn (1978). However, studies on rats (Leturque et al. 1984) and sheep (Petterson et al. 1993) showed very similar reductions in sensitivity (increased insulin concentrations required to produce half-maximal responses) of various indices of peripheral glucose utilisation in late-pregnant versus nonpregnant animals. For example, the rightward shift in the relation between insulin-dependent glucose utilisation and plasma insulin in pregnant sheep is illustrated in Figure 1. In rats, but not in sheep, sensitivity of the insulin-induced reduction in endogenous glucose production (presumably hepatic gluconeogenesis) was also markedly reduced. In both species, pregnancy-specific reductions in maximal glucose metabolic responses to insulin were absent or less evident.

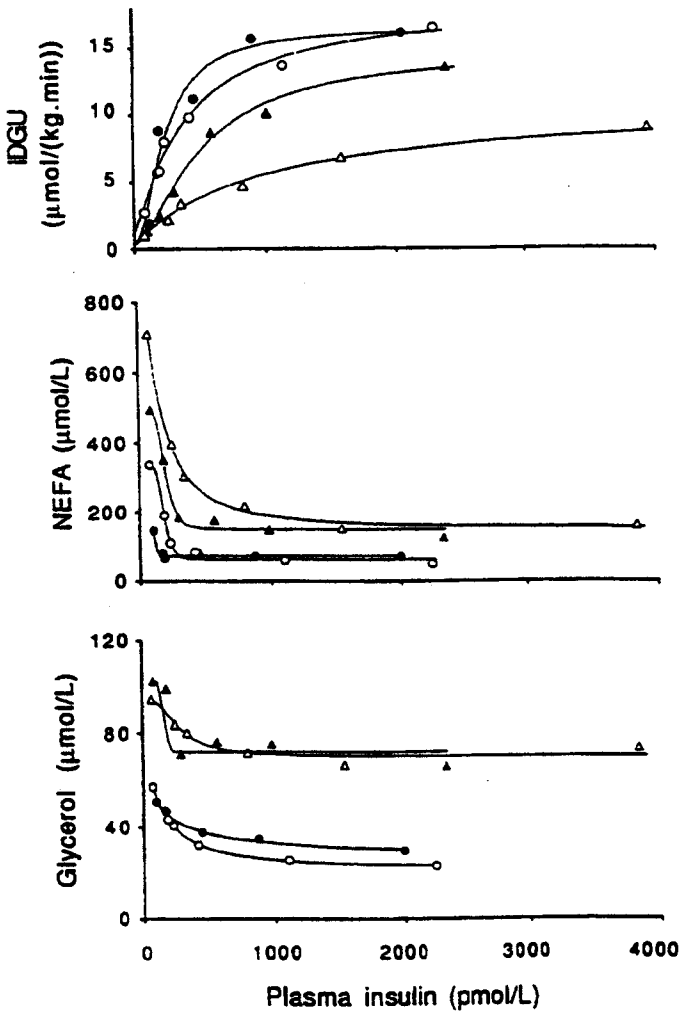

Figure 1. Effects of plasma insulin concentration under euglycaemic conditions on insulin-dependent, whole-body glucose utilisation (IDGU) and plasma concentrations of nonesterified fatty acids (NEFA) and glycerol in well-fed, nonpregnant (•), underfed, nonpregnant (o), well-fed, pregnant (s) and underfed, pregnant ewes (Δ). Adapted from Petterson et al. (1993, 1994).

According to the Kahn (1978) paradigm, decreased insulin sensitivity is most likely to be due to decreased insulin receptor activity in responsive tissues. However, this has been difficult to demonstrate in vitro in a variety of cell types, including monocytes, erythrocytes and adipocytes (Kuhl 1991). More recently, Damm et al. (1993) reported equivocal evidence for a reduction in insulin binding by vastus lateralis muscle biopsied from healthy women during late pregnancy (Figure 2). No effect on insulin receptor tyrosine kinase activity was found, consistent with a previous finding in pregnant rats (Camps et al. 1990). Therefore, the authors concluded that altered insulin receptor function in skeletal muscle is not an important contributor to the normal development of insulin resistance in this tissue during late pregnancy, as defined in studies on laboratory animals (Leturque et al. 1986; Hauguel et al. 1987). Reduced insulin sensitivity of skeletal muscle might also be explained by impairment in the insulin-dependent glucose transport system. Neither GLUT-4 protein nor mRNA abundance was reduced in skeletal muscle biopsied from women in late pregnancy (Garvey et al. 1992), but the possibility of effects on GLUT-4 translocation or activation remains open.

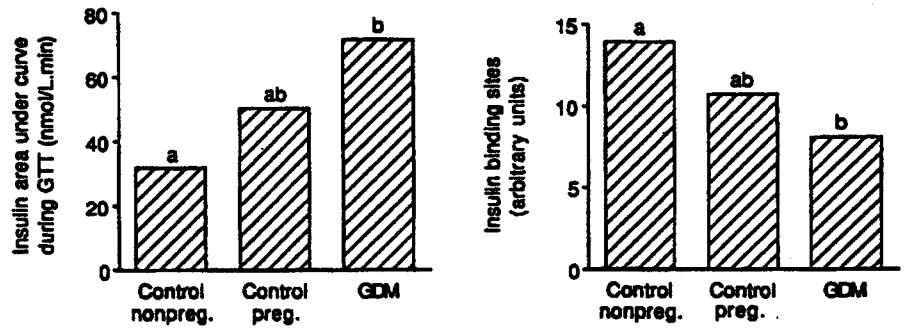

Figure 2. Plasma insulin response 0-120 min during 75g oral glucose tolerance test (GTT) (left panel), and apparent insulin receptor number in partially purified preparations from biopsied vastus lateralis muscle (right panel) in nonpregnant (n=8), normal pregnant (n=8), and gestationally diabetic (GDM, n=8), nonobese women. Values with different letters are significantly different ($P<0.05$). Adapted from Damm et al. (1993).

Effects of pregnancy on insulin-mediated glucose disposal in adipose tissue appear to vary with species, diet and other factors (Leturque et al. 1986; Andersen and Kuhl 1988), probably according to the quantitative importance of de novo fatty acid synthesis as an avenue of glucose utilisation. However, we recently reported a significant reduction in the ability of insulin to maximally suppress basal lipolysis, indicated by plasma concentrations of NEFA and glycerol, in late-pregnant versus nonpregnant ewes (Figure 1) (Petterson et al. 1994). Interestingly, the ED_{50} for this response was considerably lower than that for insulin's effects on peripheral glucose utilisation in the same animals (Petterson et al. 1993), and quite unaffected by pregnancy. This implies that in sheep, attenuation of the antilipolytic response to insulin during late pregnancy is mediated by postreceptor regulatory changes in adipose tissue, ultimately affecting hormone-sensitive lipase activity. However, at least one study indicated a reduction in insulin receptor number of adipocytes from ewes during late pregnancy (Vernon et al. 1981a).

(ii) Gestational diabetes Disagreement as to whether GDM involves the development of insulin resistance that is more severe than in normal late pregnancy can probably be reconciled by the heterogeneity of the syndrome in terms of aetiology and severity, and associated variations in diagnostic criteria. Ryan et al. (1985) observed that the insulin resistance of late pregnancy was exaggerated in women suffering GDM, judged from their more profoundly reduced glucose utilisation responses to submaximal and maximal doses of insulin. In contrast, the reduction in whole-body insulin sensitivity, assessed by the minimal model technique, was similar in women with 'mild' GDM and normal women during late pregnancy (Buchanan et al. 1990b). However, pancreatic β-cell responsiveness to glucose was impaired in the GDM group.

Notably, the tendency for insulin binding in skeletal muscle to be reduced in late pregnancy was more clearly evident in women with GDM, and was attributed to a reduction in receptor number (Figure 2) (Damm et al. 1993). However, insulin receptor tyrosine kinase activity was unchanged. The degree to which postreceptor responses to insulin in muscle are further suppressed in GDM versus normal pregnant subjects is not clear. For example, there is no evidence for altered transcriptional or translational regulation of GLUT-4 abundance in skeletal muscle of women with GDM (Garvey et al. 1992). In contrast, insulin-stimulated glucose transport in adipocytes was substantially reduced in GDM patients compared to normal women in late pregnancy (Garvey et al. 1993). This was associated with decreased abundance of GLUT-4 protein, the severity of which was bimodally distributed in the GDM group. All GDM patients exhibited abnormalities in basal and insulin-stimulated subcellular distribution of GLUT-4.

Mild energy restriction has been reported to have beneficial effects on glucose homeostasis in women with GDM (Buchanan et al. 1990a). Possible complicating effects of more severe or

prolonged undernutrition have not been studied in pregnant humans. This is a question worth pursuing because we have found that for various indices of peripheral glucose utilisation in sheep, the normal reduction in insulin sensitivity during late pregnancy was exaggerated by moderate undernutrition (60% energy requirement) for two weeks (Figure 1) (Petterson et al. 1993).

IV. HOMEORHETIC REGULATION OF PREGNANCY-ALTERED RESPONSES TO INSULIN

The concept of homeorhesis as it applies to regulation of nutrient use was elaborated by Bauman and Currie (1980). They defined homeorhesis as 'the orchestrated or coordinated changes in metabolism of body tissues to support a [dominant] physiological state'. Key features of this concept, which distinguish it from the more familiar concept of metabolic homeostasis, are its chronic nature, i.e. hours or days versus the seconds or minutes required for most examples of homeostatic regulation; its simultaneous influence on multiple tissues with apparently unrelated functions; and its mediation through altered responses to homeostatic signals such as insulin. Insulin resistance during pregnancy provides an excellent example of all three of these putative features because it develops progressively, simultaneously affects numerous organs and tissues, and is probably achieved through the actions of chronically acting hormones such as oestradiol, cortisol, prolactin, placental lactogen (PL) and growth hormone (GH).

It is tempting to assume that hormones specific to pregnancy, such as PL, or whose pattern of secretion is strongly influenced by pregnancy, such as oestradiol, play a key role in the development of insulin resistance during late pregnancy, and may thus influence the predisposition towards GDM. Indeed, many reviews and original papers on human metabolic responses to pregnancy take this for granted. However, hard evidence is slow in forthcoming for the efficacy, let alone the mechanisms of action, of placental and other hormones in modulation of insulin sensitivity and/or responsiveness in target tissues, especially skeletal muscle and adipose tissue.

The metabolic role of PL in those species which secrete it copiously during late pregnancy, including human, sheep and rat, remains obscure although it is more than 25 years since Grumbach et al. (1968) postulated that it alters maternal glucose and lipid metabolism via induction of insulin resistance. Ovine PL appears to bind specifically to receptors in maternal liver and to a lesser extent, adipose tissue (N'Guema et al. 1986), but also crossreacts with prolactin and GH receptors in maternal tissues (Byatt et al. 1992). However, neither short-term (several hours) (Handwerger et al. 1976) nor longer (36 h) treatment of nonpregnant ewes with ovine PL (Thordarson et al. 1987) caused biologically consistent or statistically convincing effects on glucose or NEFA metabolism. Also, metabolic responses to passive immunoneutralization of ovine PL in pregnant ewes were inconclusive (Waters et al. 1985). Finally, in vivo placental release of ovine PL was unchanged in moderately undernourished, late-pregnant ewes that were displaying the metabolic hallmarks of insulin resistance and partitioning of glucose to favor conceptus versus maternal tissues (Nobrega et al. 1991; Petterson et al. 1993).

Increased placental secretion and maternal plasma concentrations of oestrogens may influence glucose and lipid metabolism in late pregnancy. We have preliminary evidence that chronic treatment of nonpregnant, ovariectomized ewes with oestradiol-17β, sufficient to increase plasma levels to those of near-term ewes, causes persistent increases in plasma glucose, NEFA and glycerol (Andriguetto et al. 1995). Similar treatment of ewes in another study caused a major inhibition of in vitro capacity for adipose lipogenesis and fatty acid esterification (Green et al. 1992). Our investigations of the chronic effects of oestradiol-17β on insulin sensitivity and responsiveness in nonpregnant ewes are incomplete, but it appears that treatment caused a moderate reduction in insulin clearance, possibly associated with reduced capacity for insulin binding in insulin-responsive tissues (Andriguetto et al. unpublished data).

V. CONCLUSIONS

Development of insulin resistance during late pregnancy is a physiologically normal adaptation to ensure that the partitioning of maternal nutrients, especially glucose, favours the growing conceptus. It is curious that the magnitude of this adaptive response in humans often exceeds that in animal species in which the nutrient demands of pregnancy are much greater, with GDM representing an extreme human manifestation.

Mechanisms of insulin resistance may vary somewhat between tissues, for example, in the degree to which receptor versus postreceptor functions are altered. Much of the normal insulin resistance in lean, pregnant women is presumed to originate in skeletal muscle through impairment of insulin receptor number and intracellular capacity for glucose metabolism. It is tempting to suggest that the predisposition of obese women to GDM involves a quantitatively much greater role for impairment of insulin's actions on adipose tissue, which appear to include profound alterations in different components of the glucose transport system.

The homeorhetic regulation of insulin resistance and consequent metabolic adaptations in skeletal muscle, adipose tissue, liver and possibly other tissues in late pregnancy is likely to be a complex process, involving subtle interactions between numerous hormones, their receptors and intracellular transduction systems. Dissection and delineation of these mechanisms will require in vivo studies to investigate the multiple, extracellular influences of putative homeorhetic hormones as discussed elsewhere (Bell and Bauman 1994). At the same time, molecular studies should focus on defining precisely how such hormones might modify specific subcellular actions of insulin. Recent advances in the understanding of mechanisms for GH signal transduction (Carter-Su et al. 1994) offer an excellent example.

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