Gestational diabetes: emerging concepts in pathophysiology

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Summary: Gestational diabetes affects 3 to 5% of pregnancies in the United Kingdom, contributing to significant maternal and fetal morbidity. Understanding the pathophysiology is important as it guides diagnostic screening and treatment. The insulin resistance of normal pregnancy facilitates provision of metabolic substrates to the fetus and is multifactorial in origin. Recent identification of hepatic and skeletal muscle lipid deposition in Type 2 diabetics, demonstrated by novel magnetic resonance spectroscopy techniques, is likely to be the underlying cause of pathological insulin resistance. Similar mechanisms almost certainly underlie gestational diabetes, although further studies are required to prove this. Women who develop gestational diabetes have demonstrable insulin resistance prior to pregnancy that is part of a chronic process of lipid accumulation ultimately leading to type 2 diabetes later in life. The importance of lifestyle advice and dietary modification and the rationale behind the use of metformin are thus explained.

Keywords: gestational diabetes, obesity, insulin resistance, fatty liver disease, magnetic resonance spectroscopy

INTRODUCTION

Gestational diabetes (glucose intolerance with onset or first recognition during pregnancy) affects between 3% and 5% of pregnancies in the UK.¹ It is associated with fetal macrosomia, shoulder dystocia and neonatal hypoglycaemia. Ramifications extend well beyond pregnancy and the puerperium, with both mother and baby at increased risk of type 2 diabetes and its associated complications later in life.

There is much confusion and controversy regarding how 'glucose intolerance' is defined during pregnancy. Generally, individuals are placed into three categories: normal, impaired or diabetic. It has been debated whether 'impaired glucose tolerance' is clinically significant or simply a physiological adaptation to pregnancy. Recent data, however, have demonstrated that glucose intolerance is associated with maternal and fetal outcomes as poor as those seen in type 1 diabetes.^{2,3} Gestational diabetes, as defined by the World Health Organization, now includes any level of glucose intolerance from just impaired to frankly 'diabetic'.⁴ The Hyperglycaemia and Adverse Pregnancy Outcome study, a multicentred observational study of approximately 25,000 women with impaired glucose tolerance from a diverse multicultural background, showed a positive correlation between higher maternal glucose and the frequency of adverse perinatal outcome.⁵ As a result, in 2008, the International Association of Diabetes and Pregnancy Study Groups formulated new diagnostic thresholds for gestational diabetes (Table 1).⁶

MEASURING GLUCOSE INTOLERANCE

The oral glucose tolerance test (OGTT) is used to diagnose gestational diabetes. This consists of a fasting glucose sample, administration of a glucose load (usually in the form of a glucose drink) and repeated samples after a specified time interval. A 75 g glucose load and two-hour OGTT is standard in Europe and Australasia, whereas a 100 g glucose load and three-hour sampling is used in North America. The reference ranges for each depend upon the type of blood glucose sample taken. Current diagnostic criteria for gestational diabetes are summarized in Table 1. Capillary (or arterial) blood has a higher glucose content than venous blood since the tissues absorb and utilize glucose. Given such widespread variations in performing a straightforward test, it is easy to see how confusing the identification of gestational diabetes has become. Furthermore, knowing *when* in pregnancy to test for gestational diabetes is critical. To answer this question requires knowledge of both the insulin resistance of normal pregnancy and the pathophysiology of gestational diabetes.

ACTION OF INSULIN

Insulin is produced by the beta cells of the pancreas in response to elevated blood glucose concentrations. It acts on many cells, primarily liver, muscle and adipose tissue via an insulin receptor. The binding of insulin triggers various downstream intracellular pathways, the first of which is phosphorylation of the insulin receptor and activation of insulin receptor substrate-1, ultimately leading to:

- (1) Glucose uptake;
- (2) Storage of glycogen, fat and protein;
- (3) Inhibition of glucose, amino acid and fatty acid production.

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Table 1 Thresholds for diagnosing gestational diabetes

	World Health Organization*	American Diabetes Association [†]	IADPSG* [‡]
Glucose load (g)	75	100	75
Venous plasma glucose level (mmol/L)			
Fasting	7.0	5.3	5.1
1 hour		10.0	10.0
2 hours	7.8	8.6	8.5
3 hours		7.8	

*One or more of the values to be met or exceeded for a diagnosis
[†]Two or more of the values to be met or exceeded for a diagnosis
[‡]IADPSG: International Association Diabetes in Pregnancy Study Group^{1,4,6}

The fetus requires a constant supply of nutrients in the form of glucose, fatty acids and amino acids. Insulin resistance is therefore a consequence of fetal demands where availability of metabolic substrates is prioritized over maternal storage.

INSULIN RESISTANCE IN NORMAL PREGNANCY

A steady reduction in insulin sensitivity occurs from 18 to approximately 28 weeks gestation (Figures 1 and 2).^{7,8} Following delivery, insulin sensitivity returns to prepregnancy levels. It is unclear how insulin resistance occurs, but several factors are likely to play contributory roles.

Hormones

Sensitivity to insulin decreases progressively during pregnancy and swiftly returns to normal following delivery, strongly suggesting a hormonal association. In particular, human placental lactogen, human placental growth hormone, progesterone, cortisol and prolactin are known to counteract the effects of insulin.⁹ Although reproductive hormones are frequently cited as the cause for insulin resistance, changes in

Figure 1 Longitudinal changes in insulin sensitivity during a euglycaemic-hyperinsulinaemic clamp study (mean ± SD). GDM = gestational diabetes mellitus; P_t = P value for individual longitudinal changes with time; P_g = P value for difference between groups (adapted from Catalano PM, *et al.*³⁴)

Figure 2 The time course of change in insulin sensitivity during pregnancy is reflected by the change in exogenous insulin dose required to maintain glucose control in type 1 diabetes. The figure shows change in mean insulin daily dose requirement in 107 consecutive type 1 diabetic pregnancies⁸

hormone concentrations do not directly correlate with insulin resistance.¹⁰ The relationship between such hormones and insulin action may not be simple cause and effect.

Inflammation

Normal pregnancy is a proinflammatory state. Tumour necrosis factor alpha (TNF- α), an adipo-cytokine, has been shown to promote insulin resistance through its prohibitive action on the insulin receptor. Elevation of TNF- α in pregnancy correlates with progressive insulin resistance.¹⁰ Additionally, elevated levels of TNF- α have been found in conditions associated with hyperinsulinaemia such as obesity and type 2 diabetes.¹¹ However, the degree of increase of TNF- α levels is very small in comparison with that seen in infection or after major trauma, and neutralization of TNF- α with monoclonal antibodies has no effect on insulin resistance in people with type 2 diabetes, implying that while TNF- α may contribute to insulin resistance, it is by no means the single causative factor.¹²

Adipose-derived hormones

Adiponectin is a globular protein synthesized by adipose tissue. It belongs to a group of hormones, including leptin and resistin, that control local storage and distribution of fat. Low adiponectin concentrations correlate with insulin resistant states.¹³ Adiponectin stimulates glucose uptake in skeletal muscle and inhibits hepatic glucose production. Studies have shown that adiponectin levels decline with advancing gestation in normal pregnancy and are further reduced in gestational diabetes.^{14,15} However, the changes are small and unlikely to confer any major effect.

Fat deposition

Pregnancy is associated with increased maternal adiposity and storage of carbohydrate and fat, perhaps as an evolutionary adaptation to facilitate successful lactation. Studies of people with type 2 diabetes have identified that fat deposition within skeletal muscle and liver cells is a major contributory factor to insulin resistance.¹⁶ It is unknown whether fat deposition during pregnancy explains the acquisition of insulin resistance.

INSULIN RESISTANCE IN TYPE 2 DIABETES

Type 2 diabetes is closely related to gestational diabetes. People who acquire these forms of diabetes share the same risk factors: ethnicity (South Asian or Afro-Caribbean), raised body mass index (BMI), advanced age, family history and polycystic ovary disease. Furthermore, a significant proportion of women with gestational diabetes develop type 2 diabetes later in life.¹⁷ Finally, progressive insulin resistance is a hallmark of both diseases. It would therefore be reasonable to reflect on the advances that have been made towards understanding type 2 diabetes and examine whether these are relevant to gestational diabetes.

Magnetic resonance spectroscopy (MRS) has enabled us to study biochemical tissue changes *in vivo* without the need for invasive organ biopsies. Emerging from this technology is the revelation that lipid plays a critical role in insulin resistance in competing with glucose for oxidation. This moves us forward from a glucose-only model of diabetes to one incorporating lipid metabolism, and from a narrow focus on insulin signalling to recognition of the role of substrate competition.¹⁸

Western diet and lifestyle predisposes to a calorie intake that exceeds expenditure. As energy is converted into fat and stored, obesity is the result. Not only is fat deposited in adipose tissue but a significant proportion is also stored in the viscera, specifically the liver, heart, blood vessels and muscle. The liver, which processes blood rich in metabolites from the gut, is perhaps the organ most at risk of excess fat accumulation. A fatty liver is strongly associated with obesity and can develop rapidly, such that it is increasingly common to see this condition in children and adolescents.¹⁹ Under the influence of insulin and calorie excess, glucose is converted to fatty acids within the liver. These may be metabolized or stored in the liver as triglyceride or repackaged as very-low-density lipoproteins (VLDL) and transported elsewhere. Under conditions of energy surplus, not all fatty acid is metabolized, with consequent storage as fat or conversion to VLDL.

An important feature of liver metabolism is to provide the body with a source of glucose during periods of starvation. Hepatic glucose production is either achieved through breakdown of glycogen (glycolysis) or production of glucose from other metabolites (gluconeogenesis). In lean individuals who do not have diabetes, insulin inhibits hepatic glucose production entirely. In the presence of fatty liver, however, inhibition is lost and blood glucose levels are elevated resulting in a 2.5-fold increase in insulin production to achieve glucose homeostasis.²⁰ Hyperinsulinaemia promotes further liver triglyceride deposition and a vicious circle of fat deposition, insulin resistance, elevated blood glucose and hyperinsulinaemia ensues (Figure 3). Development of diabetes occurs when insulin production cannot overcome insulin resistance.

Figure 3 The twin vicious cycles leading to hyperglycaemia (adapted from Taylor R³⁵)

Changes in regulation of hepatic glucose production in normal pregnancy are similar to type 2 diabetes. Insulin is unable to suppress glucose production which increases by around 30% compared with the non-pregnant state.²¹ This reflects the needs of the fetus and placenta, which together account for around half of hepatic glucose production in late pregnancy. Interestingly, this increase is similar for lean and obese women and women with gestational diabetes. However, the amount of insulin required to suppress hepatic glucose production is disproportionately elevated in women with gestational diabetes. Consequently, a three-fold increase in basal insulin levels is required to maintain glucose homeostasis compared with obese controls.⁷ There is also failure to suppress hepatic glucose production even with very high levels of insulin treatment. This evidence supports the concept that hepatic insulin resistance occurs in normal pregnancy and is exacerbated in gestational diabetes.

The link between hepatic insulin resistance and raised intrahepatic lipid deposition has not been studied in human pregnancy. Animal models have shown that pregnancy causes a two-fold increase in intrahepatic triglyceride.²² Follow-up studies in non-pregnant women with a previous history of gestational diabetes have shown that those with a high liver fat content ($9.8 \pm 1.5\%$) as measured by MRS had higher insulin resistance and elevated basal insulin concentrations than controls with low liver fat content ($3.2 \pm 0.3\%$).²³

LIPID DEPOSITION IN MUSCLE

Skeletal muscle is a major source of glucose uptake and metabolism. Fat deposition within muscle fibres (intramyocellular lipid) reflects intrahepatic lipid.^{24,25} MRS studies have demonstrated a negative correlation between intramyocellular lipid deposition and insulin sensitivity and it is likely that this is the cause of insulin resistance in muscle.²⁶ Little is known about the effects of pregnancy on intramyocellular lipid deposition; however, this is currently the subject of an ongoing study.

A case-control study demonstrated that women who were between four and six months following a pregnancy complicated by gestational diabetes have a 35% reduction in insulin sensitivity and a 60% increase in intramyocellular lipid content compared with controls.²⁷ Women who required insulin treatment during pregnancy had substantially elevated intramyocellular lipid content compared with those controlled

through diet alone. It can be concluded that either pregnancy increases intramyocellular lipid deposition and that these changes persist postpartum, or more likely, that intramyocellular lipid deposition predates the pregnancy and continues postpartum. Thus, both intrahepatic and intramyocellular lipid deposition are key contributors to the progression of insulin resistance in type 2 diabetes, although it is likely that similar mechanisms underlie gestational diabetes. Further studies are required to confirm this.

INSULIN SECRETION

Robust beta-cell function is essential for glucose regulation. This becomes particularly important in the face of insulin resistance. During normal pregnancy there is a rapid insulin rise in response to insulin resistance (Figure 4). Women with gestational diabetes, however, are unable to up-regulate insulin production relative to the degree of insulin resistance, and become hyperglycaemic.²⁸

Pregnancy is therefore a test of beta cell reserve: if there is good function insulin resistance will be overcome, otherwise gestational diabetes results. Insulin production is similarly deficient in type 2 diabetes. Lipid deposition, this time within the pancreas, may explain the pathophysiology.²⁹

TESTING FOR GESTATIONAL DIABETES

Women who develop gestational diabetes have demonstrable insulin resistance prior to pregnancy.³⁰ It is probable that this is part of a chronic process of lipid accumulation that ultimately leads to type 2 diabetes later in life. Pregnancy unleashes a burden of extra insulin resistance and a deficit in beta cell function that results in gestational diabetes.

National Institute for Clinical Excellence guidelines recommend screening women for gestational diabetes with the following risk factors: BMI above 30, previous macrosomic baby weighing 4.5 kg or above, previous gestational diabetes, first-degree relative with diabetes and family origin with a high prevalence of diabetes. Screening includes an OGTT at 16–18 weeks, if the woman has a prior history of gestational diabetes, followed by OGTT at 28 weeks if the first test is normal; or an OGTT at 24–28 weeks if there is any other risk factor.³¹ Although this is likely to detect most cases of

gestational diabetes, it is important to recognize that these guidelines will miss women with insulin resistance outside the 'high-risk' group.

IMPLICATIONS FOR TREATING GESTATIONAL DIABETES

Understanding the pathophysiology of gestational diabetes is important as it provides a rational basis for the lifestyle advice and dietary modification. Both exercise and weight loss, even in modest amounts, reduce fatty liver and improve insulin resistance.³²

To date, insulin therapy has been the main pharmacological method of controlling hyperglycaemia in gestational diabetes. It has the advantage of not crossing the placenta. The use of metformin to treat gestational diabetes is a relatively recent advance. Neonatal outcomes are equivalent to supplementary insulin and therapy is better tolerated by women.³³ Metformin enhances suppression of hepatic glucose production, thereby inhibiting the critical pathological process that leads to gestational diabetes. Sulphonylureas increase portal vein insulin levels and hence are likely to promote hepatic lipid deposition. From the maternal perspective, metformin should, therefore, be the drug of first choice, with supplementary insulin added where necessary to achieve glycaemic control. Other drugs that improve insulin sensitivity could theoretically be of use in gestational diabetes. Further data regarding the long-term paediatric effects of these agents are awaited.

CONCLUSION

Evidence that gestational and type 2 diabetes share the same pathophysiology is compelling. However, further work is required to fully define the pathophysiology of gestational diabetes. MRS may provide the technology to define the role of intra-organ lipid deposition in human pregnancy with or without gestational diabetes. Such understanding will be fundamental to future therapeutic advances.

Conflict of interest: None declared.

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Figure 4 Beta cell response to insulin resistance (adapted from Buchanan TA, et al.²⁸)

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