Gestational diabetes: an analysis

Gestational diabetes: consequences for fetal programming of vascular disease in adulthood

List of Abbreviations

AGE Advanced Glycation End Products

CNS- Central Nervous System

EDHF- Endothelium-Derived Hyperpolarising Factor

eNOS Endothelium derived Nitric Oxide

ECM- Extra Cellular Matrix

FFA Free Fatty Acids

GAD 65- Glutamic Acid Decarboxylase

GDM-Gestational Diabetes Mellitus

HDL- High Density Lipoprotein

HPL- Human Placental Lactogen

IA-2 Insulinoma- Associated Antigen 2

ICA- Islet Cell Antibody

IRS-1 Insulin Receptor Substrate 1

IUGR – Intrauterine Growth Restriction

LDL- Low Density Lipoprotein

MODY- Maturity Onset Disease of the Young

MRS- Magnetic Resonance Spectroscopy

NO Nitric Oxide

OS- Oxidative Stress

PKC- Protein Kinase C

ROS Reactive Oxygen species

TNF-α- Tumour Necrosis Factor α

T1D Type 1 Diabetes

T2D Type 2 Diabetes

ZnT8 Zinc Transporter

5-HT Serotonin

Abstract

Gestational Diabetes is a condition present in the later stages of pregnancy where the mother has insulin resistance leading to glucose intolerance. The aetiology of Gestational Diabetes Mellitus is largely unknown but several theories include autoimmune destruction of the beta cells, monogenic mutations and insulin resistance. In pregnancy it is normal for there to be some levels of insulin resistance and it is thought that the products of the placenta contribute to the state of insulin resistance as GDM usually subsides after pregnancy. GDM in pregnancy can lead to an increased risk of cardiovascular disease in the offspring such as hypertension and atherosclerosis. This is due to the increased levels of oxidative stress and

inflammatory mediators present during pregnancy. The placenta is very important as it is able to control and buffer the amount of glucose that is delivered to the fetus but if this level is too high then it is out of the placenta’s control and the fetus may have increased rate of growth due to this extra glucose. The current focus of research in this area seems to be into finding ways to diagnosis GDM earlier in the pregnancy and to try and reduce the amounts of oxidative stress.

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Introduction

Gestational Diabetes Mellitus (GDM) occurs when there is a glucose intolerance that is first detected during pregnancy. It is a form of hyperglycaemia (Buchanan and Xiang 2005). The aetiology of the condition is unknown but there have been many suggestions as to the cause of it, including autoimmune destruction of the β pancreatic cells and the possibility of a genetic predisposition to the condition. Hormones that are produced in pregnancy help contribute to the insulin resistant state which characterises diabetes. In recent years, there has been an increase in the cases of Obesity and this is a risk factor for both Diabetes Mellitus and Cardiovascular Disease. The intrauterine environment can affect fetal programming and development. This essay will look into how the placenta and its products can affect the insulin resistant state and how this resistance effects programming as well as the role of oxidative stress and inflammation in making the offspring more susceptible to cardiovascular disease.

Gestational Diabetes Mellitus (GDM)

GDM is a state of insulin resistance which disturbs the intrauterine environment and can lead to accelerated fetal growth (Radaelli et al 2003). It effects approximately 7% of pregnant women with approximately 200, 000 cases seen each year (Schillan-Koliopoulos and Guadagno 2006). The term GDM is applicable when the onset is during the second and third terms of the pregnancy, but it does not exclude the possibility that the insulin resistance was undiagnosed before the pregnancy. If this is the case and is found to occur in the earlier stages of pregnancy then the mother should be treated the same as mothers who are known to have diabetes before pregnancy (Metzger, Coustan 1998).

There is a degree of insulin resistance in normal pregnancy which begins towards the middle of the pregnancy but during the later part of the second and the final trimester these can increase to levels of insulin resistance that are associated with type 2 diabetes (Yogev et al 2008 Chapter 10). Insulin resistance is when the tissues do not produce a response to insulin due to problems with the secretion of insulin or where the tissues are desensitised to insulin and therefore lack the ability to produce a response (Catalano et al 2003).

In a normal pregnancy, the mother changes her metabolism to allow a constant supply of nutrients to reach the fetus to support its rapid growth. Among these nutrients is glucose, which is the main energy source used by the fetus. During the later stages of pregnancy the mother becomes hypoglycaemic and although there is increased gluconeogenesis, the hypoglycaemia still occurs because there is a high rate of transport of

glucose to the fetus (Herrera 2000 cited in Herrera and Ortega 2008). GDM can have effects that impact the development of the fetus such as hypoglycaemia and macrosomia, which is an increase in body weight and has the possibility of leading to problems when giving birth, such as shoulder dystocia (Schillan-Koliopoulos and Guadagno 2006). During the second trimester of pregnancy there is peripheral insulin resistance but there is also the possibility that hepatic insulin sensitivity is altered in pregnancy, although few studies confirm this. By the end of the pregnancy the levels of insulin that are circulating are thought to be double those at the start (Redman 2001).

Insulin Resistance

Insulin resistance in GDM can occur in two forms. The first is where it develops in late pregnancy and it has been postulated that there is a post-receptor mechanism that may influence the insulin signalling pathway which leads to a reduced glucose uptake. The second form is where there is already a degree of resistance before the pregnancy but the changes that occur in normal pregnancy aggravate this (Metznger et al 2007). The insulin resistance that develops in pregnancy is much needed to allow the flow of nutrients, from the mother, directly to the fetus to allow for growth (Radaelli 2003). Increased insulin resistance leads to an increase in insulin secretion by the β pancreatic cells (Buchanan and Xiang 2005).

The insulin resistance is thought to be caused by increased adiposity and as the insulin resistance usually stops after pregnancy this suggests that there is a possibility that the products of the placenta are a potential cause of the resistance. During the course of the pregnancy the actual changes in glucose

levels are very small. It would be assumed that the glucose levels would rise due to the increased insulin resistance but the pancreatic β cells increase their secretion of insulin to maintain homeostatic glucose levels (Yogev et al 2008 Chapter 10).

GDM occurs because there is an increased demand for insulin which under normal circumstances can be met unless there are problems with the secretion of insulin leading to the development of hyperglycaemia. The majority of mothers who develop GDM have been discovered to have a degree of insulin resistance before they became pregnant. Therefore, with the insulin resistance that occurs in normal pregnancy it can be said that GDM occurs with a greater insulin resistance than normally present in gestation (Yogev et al 2008 Chapter 10). Insulin resistance causes a decreased uptake of glucose into skeletal muscle, adipose tissue and liver as well as a decreased production of hepatic glucose. (Catalano et al 2003).

One suggestion for insulin resistance looks into the possible role of the mitochondria. Studies using Magnetic Resonance Spectroscopy (MRS) have shown that in normal offspring of parents with type 2 diabetes, there is an increased amount of intramyocellular lipid. This has been shown to cause a reduced function in mitochondria which suggests that mitochondrial dysfunction may play a part in insulin resistance (Petersen et al 2004 cited in Morino et al 2005). It has been suggested that this increase in intramyocellular lipid activates a serine kinase cascade which causes an increase in the Insulin Substrate Receptor 1 (IRS-1), which inhibits insulin receptor phosphorylation on tyrosine sites. This can cause a decrease in the effects and utilisation of glucose. One study showed that in the insulin

resistant offspring the mitochondrial density was reduced by just over a third to that of a normal offspring. This suggests that offspring who are insulin resistant may inherit a condition that causes a reduction in rate oxidative phosphorylation in mitochondria (Griffin et al 2009 cited in Morino et al 2005).

Detection of GDM

Diagnosis of GDM helps to identify pregnancies that are at risk of fetal morbidity as well as obesity and glucose intolerance in the offspring (Buchanan and Xiang 2005). GDM is hard to diagnose as it is asymptomatic. Normal diabetes could be diagnosed by glycosuria but in pregnancy the renal threshold to glucose is lowered so that glycosuria doesn't give a true representation of hyperglycaemia (Redman 2001). There are several risk factors of GDM which can be classified into three groups and help in the screening process. Low risk factors include women who are younger than 25, normal weight at conception, no known family members with diabetes and no history of glucose intolerance. High risk factors include obesity of the mother, diabetes in close relatives, a history of glucose intolerance, current glycosuria and previous pregnancies with GDM (Metzger and Coustan 1998 Chapter 25).

Causes of Diabetes

There are several theories as to why diabetes occurs and this has been thought to be similar to the underlying mechanisms that cause gestational diabetes. Diabetes is a result of pancreatic beta-cell dysfunction which can present in three main ways: autoimmune, a genetic cause and on top of already present insulin resistance (Buchanan and Xiang 2005).

Autoimmune diabetes accounts for approximately 5-10% of all diabetic cases (American Diabetes Association 2010). There are circulating antibodies to the β cells of the Islet of Langerhans. In GDM, there are a small number of women who have with these antibodies present in their circulation. It is thought that these cases present with GDM due to problems with insulin secretion caused by destruction of the Islets by the autoantibodies (Buchanan and Xiang 2005). This form is similar to type 1 diabetes. The Islet Cell Autoantibodies' (ICA) have been shown to have four major molecular targets: Insulin, Glutamic acid decarboxylase (GAD 65), Insulinoma-associated antigen-2 (IA-2) and Zinc Transporter 8 (ZnT8) (Tree 2010).

Monogenic diabetes has 2 general forms, one where there are mutations in autosomes and the other where there are mutations in the DNA of mitochondria. The first form is commonly referred to as Maturity Onset Diabetes of the Young (MODY). In both cases onset tends to be at a young age and the patient doesn't present with insulin resistance or obesity (Buchanan and Xiang 2005). Mutations that cause MODY have been found in some women with GDM and commonly occur in genes coding for glucokinase, hepatocyte nuclear factor and insulin promoter factor, MODY is associated with beta cell dysfunction (Weng et al 2002).

Chronic insulin resistance with beta-cell dysfunction seems to be the most common cause of GDM. As mentioned before there is an increase in insulin resistance in normal pregnancy but if this develops with background insulin resistance then there is an even greater insulin resistance which can lead to GDM. An established suggestion is that women who are unable to increase their secretion of insulin to cope with the insulin resistance developed in late

pregnancy are more susceptible to developing GDM (Buchanan and Xiang 2005).

However there could be various environmental processes that are involved in the underlying pathophysiology of GDM. The products of the placenta may also have a role in increasing or decreasing insulin resistance and these will be discussed later.

Placental Function

The placenta is an organ that has many roles during the development of the fetus. One of these functions is that it acts as a barrier to separate the maternal and fetal surfaces such that the syncytiotrophoblast surface exposes the placenta to the maternal circulation and the endothelium is exposed to the fetal circulation. This position between the two circulations means that the placenta is influenced by molecules from both circulatory systems, including cytokines, hormones and growth factors. The placenta produces molecules which can separately affect the maternal and fetal circulation and it expresses a large number of cytokines including leptin, resistin and tumour necrosis factor. However it has been discovered that these molecules are also produced by adipocytes. All molecules that are going from the mother to the fetus have to cross the placenta. Here they are either modified, for example lipids or like glucose, they are metabolised for placental purposes (Desoye et al 2008).

The placenta plays an important role in fetal growth and the regulation of pregnancy (Giachini 2008). The placenta acts to sustain normal homeostatic levels and to carry out the functions of the vital organs. It also provides an

immunological defence to the fetus and allows the exchange of molecules vital to its development (Jansson and Taylor 2007).

Placental Development

Approximately 4-5 days after conception, the process of cleavage causes rapid cell divisions and one of the groups of cells to form are called trophoblast cells. Further developmental processes form the blastocyte which is surrounded by an outer layer of the trophoblast cells. As the pregnancy progresses, the trophoblast cells develop into the placenta while the inner parts of the blastocyte form the embryo and umbilical cord (Huppertz 2008).

The blastocyte implants itself onto the epithelium of the uterus where it differentiates into a syncitiotrophoblast which is able to implant itself in the epithelium leading to it being embedded into the decidual part of the uterus (Huppertz 2008). After the attachment of the blastocyte, the trophoblast layer divides very quickly and changes into 2 layers; the inner cytotrophoblastic layer and the outer syncytiotrophoblastic mass (Gude et al 2004). The whole implantation process takes 12 days to complete and after this the fetus is fully embedded into the endometrial layer (Huppertz 2008).

The chorionic plate is the surface of the placenta that faces the fetus and this is where the umbilical cord inserts. The basal plate is the surface that faces the mother which contains many types of cells including immune cells such as macrophages and killer cells to carry out the placentas immunological function. The maternal basal plate and the fetal chorionic

plate converge to form the smooth chorion which is composed of three layers (Huppertz 2008).

When the trophopblast invades the endothelium there is a remodelling of the uterine spinal arteries which is necessary to ensure that the fetus and the placenta receive an adequate blood and nutrient supply and is able to remove any waste materials. This direct supply of blood and nutrients to the placenta can define it as being haemochorial villous organ (Gude et al 2004).

After the rapid divisions of the trophoblast and development into 2 layers there are two pathways that can occur, the villous and extravillious pathways. The extravillious pathway results in the trophoblast being able to invade into the decidua and cause the remodelling of the uterine arteries to increase blood supply to the placento-fetal unit. The villious pathway has a transportation function as well as having endocrine and protective functions (Gude et al 2004).

Normal Placentation

Placentation involves the structure and function of the placenta. The process of placentation is helped by the composition and arrangement of the extracellular matrix (ECM) of the endometrium. Studies on rats induced with diabetes provided results that showed that diabetes has an effect on the distribution of the ECM molecules. This study by Giachini et al illustrates that Types I and III collagen as well as other molecules, such as proteoglycan molecules decorin and biglycan were distributed throughout normal and diabetic placentas. It was shown that diabetes affects the expression of fibronectin and an increase in deposition of fibronectin may cause changes

to the ECM structure which could affect the transfer of molecules from the mother to the fetus. One way in which changes in the ECM can be overcome is to test blood glucose levels frequently during the pregnancy and if kept in normal ranges this can dramatically decrease the prevalence of diseases and disorders present in the fetus (Giachini et al 2008).

As the pregnancy progresses the size of the placenta increases which also means an increase in the amount of products that the placenta produces therefore increasing in the insulin resistance (Schillan-Koliopoulos and Guadagno 2006). This is because the net effect of the products of the placenta is to increase insulin resistance.

The increase in size of the placenta means that it needs an increased blood supply. Failure of the mother to increase its blood supply to the placenta can lead to placental insuffiency which if exacerbated can be attributed to be a cause of intrauterine growth restriction (IUGR). This growth restriction is more related to poor maternal nutrition rather than to a cause of GDM. GDM have been associated with an increased fetal and placental weight (Jansson and Taylor 2007).

One of the reasons why GDM and increased insulin resistance affects the fetus is that while glucose can cross the placenta, insulin is unable to. This means that the fetal pancreas has to compensate by producing more insulin to prevent high blood glucose levels. The fetal pancreas is capable of doing this and the liver responds to the higher levels of insulin by increasing its production of glucose (Schillan-Koliopoulos and Guadagno 2006).

Offspring who have an increase in birth weight have been shown to be at risk of developing cardiovascular disease and diabetes later in life. The main risk factor for this is poor transfer of nutrients via the placenta (Jansson and Taylor 2007). How dramatic these changes are depends on how good the control of blood glucose levels have been during the development of the placenta, if any treatment has been received and if there were any periods of away from normal glucose levels (Desoye 2006).

How does diabetes affect Placentation?

Diabetic insults at the beginning of the pregnancy can have long last effects of the placenta. One of the roles of the placenta is that it is able to buffer excess maternal glucose which can help to keep the fetal glucose levels within range However if the insult lasts longer than the placenta is able to compensate for then excessive fetal growth may occur (Desoye Mouzon 2007).

In diabetes there is endothelial dysfunction which can lead to vascular disease. The endothelial cells help to control the vascular tone of the smooth muscle lining the vasculature. They do this by producing substances that help to vasodilate the smooth muscle including Nitric Oxide, Prostacyclin and Endothelium-Derived Hyperpolarising Factor (EDHF). There have been several studies to suggest different mechanisms of how diabetes affects the endothelium including impaired release of these vasodilating molecules, faults with signal transduction and increased release of constricting mediators of the endothelium. The dysfunction of the endothelium in diabetes is thought to be caused by activation of protein kinase C (PKC) as well as increased oxidative stress, non-enzymatic glycation and an increased

activation of the polyol pathway (De Vries et al 2000). The main reason why these effects occur is thought to be due the activation of the protein kinase C pathway and the increased oxidative stress. This can cause early damage to the development of vascular vessels (Roberts and Raspollini 2008). These mechanisms will be discussed later.

The effect of hormones produced in pregnancy

Pregnancy causes changes in the circulating hormones and cytokines which can all have different effects on insulin resistance and this may help explain the mechanism underlying the resistance that is found in pregnancy and in GDM.

Cytokines produced in pregnancy, such as TNF-α, Adiponectin and Leptin have been found to cause an increase in the insulin resistance (Gao et al 2008). In early pregnancy, the levels of oestrogen and progesterone rise but no net effect is seen as the two have antagonistic effects. Oestrogen increases the binding of insulin to its receptor whereas progesterone reduces the ability of insulin to bind (Ryan and Enns 1988).

Cortisol levels in pregnancy increase so that by the end of the pregnancy the levels are three times that of what they were at the beginning (Gibson and Tulchinski 1980 cited in Yogev et al Chapter 10). Studies have shown that with increased amounts of cortisol there was a decrease in insulin sensitivity causing insulin resistance (Rizza et al 1982 cited in Yogev et al 2008 chapter 10). During pregnancy the levels of prolactin increase up to ten times the normal amount (Yogev et al 2008 chapter 10). Studies have shown that in a culture of pancreatic beta cells, prolactin can cause an increase in levels of

secreted insulin (Sorenson et al 1993 cited in Yogev et al 2008 Chapter 10). However, high levels of prolactin are not seen to be a pathological cause of GDM (Yogev et al 2008 chapter 10).

Human placental lactogen (HPL) is a hormone, and its levels rise during the second trimester of pregnancy. This causes a decrease in the phosphorylation of insulin receptor substrate (IRS1) which can lead to significant insulin resistance (Ryan and Enns 2008 cited Yogev et al 2008 ch 10).

Leptin is associated with obesity and concentrations of leptin have been shown to be related to the concentration of insulin in the plasma. In pregnancy the leptin levels increase dramatically. During pregnancy the mother uses her fat stores to support fetal growth and it is thought that the leptin levels increase with the mobilisation of these fat stores. Leptin levels relate to the body mass of the individual (Sattar et al 1998). Placental Leptin is the same in structure and charge to the one produced by adipose tissue (Ashworth et al 2000). One study showed that high leptin concentrations in the umbilical cord increased the likelihood of developing fetal macrosomia (Wiznitzer et al 2000). It is also thought that leptin effects insulin sensitivity by effecting glucose metabolism in both skeletal muscle and in hepatocytes. Rats that received an external source of leptin were found to have an increase in gluconeogenesis which accounted for the majority of hepatic glucose production (Rossetti et al 1997).

In GDM there is a greater secretion of TNF-alpha in response to glucose. TNF-alpha functions to regulate metabolism of glucose and lipids as well as being

involved in insulin resistance. Many studies suggest that TNF-alpha is involved in the progression to GDM. They found that an increase in glucose cause the placenta and adipose tissue to increase production of TNF-alpha in some cases up to 4 times more than non-diabetic pregnant(Coughlan et al 2001). One study showed that the increases in the levels of TNF-alpha during pregnancy increased consistently with increases in body weight (Catalano et al cited in Yogev et al 2008).

Adiponectin is a protein derived from adipose tissue and its function is to regulate insulin resistance and maintains levels of glucose. During pregnancy it has been found that its levels drop and could therefore lead to the increase insulin resistance found in GDM (Gao, Yang, Zao 2008). Adiponectin has also been found to decrease the secretion of TNF-alpha which as stated above can lead to insulin resistance (Hotamisligil 1999 cited in Yogev et al Chapter 10 2008). Adiponectin may cause increased insulin sensitivity as its concentration decreases throughout the gestational period (Desoye and Mouzon 2007).

Resistin is a protein that is produced by adipose tissue and is thought to be involved in insulin resistance in diabetes and is associated with obesity (Steppan and Lazar 2002) In pregnancy, resistin is secreted by the placenta and this secretion reaches its peak by the last trimester (Yura et al cited in Megia et al 2008).

Studies show that TNF-alpha is an important factor in insulin resistance during pregnancy and with inputs from leptin and cortisol there is altered

glucose metabolism whereas inputs from oestrogen, progesterone and prolactin had little significant effects (Kirwan and Mouzon 2002).

There are many hormones produced during pregnancy, mainly by the placenta and adipose tissue that have varying affects but with the overall impact being insulin resistance.

Inflammation in Diabetes

There are genes in the placenta which regulate reorganisation of the endothelium and inflammatory responses and in GDM these were found to be altered. The increase in leptin receptors suggests that in the placenta this can cause proinflammatory responses (Radaelli 2003).

One of the current theories is that the abnormal metabolic environment in GDM can lead to increased production of cytokines and inflammatory mediators. Molecules such as TNF-alpha, Resistin and Leptin increase during pregnancy and these increases in these inflammatory mediators produce metabolic changes by increasing insulin resistance (Desoye and Mouzon 2007).

Leptin and TNF-alpha activate phospholipase A2 which are a family of eicosanoid precursors that go on to produce essential fatty acids such as w3 polyunsaturated fatty acids (Desoye Mouzon 2007). There has been a recent investigation which found that with increased adiposity at birth there has been an increase in w3 fatty acids in the placenta (Verastehpour et al 2005 cited Desoye and Mouzon 2007).

As stated before, the placenta produces cytokines but it is also a site of action of the cytokines. It is the location of the receptors for these cytokines will influence if the cytokines act on the mother, the placenta or the fetus. With cytokines there is very little transfer across the placenta from mother to fetus and the origin of the cytokines in the fetus can be from either the placenta or from the fetus itself (Desoye and Mouzon 2007).

Fetal Programming

Many studies have highlighted the fact that events that occur while the fetus is developing can alter its developmental pathway and have adverse outcomes in later life.

Fetal programming describes how the environment can affect certain developmental events of which the effects are permanent and can affect processes such as metabolism and the organism’s physiology. Women with GDM have an increased risk of the fetus developing macrosomia (Catalano 2008 Chapter 11).

The main factor that effects the growth of the fetus is the maternal environment and there is a strong association with the weight and height of the mother and the growth of the fetus such that mothers who are heavier and taller will produce heavy babies. (Love and Kinch 1965 cited in Catalano 2008 Chapter 11).

The placenta and fetal programming

The placenta is very important to the developmental processes of the fetus as it is able to change the quantity of signals and nutrients that the fetus receives. Deviation from normal would alter the fetal programming, thus

making it more susceptible to disease in later life. Pregnancies that are complicated by GDM have excessive oxidative and nitrate stress which has been found to change the activity of certain proteins. Oxidative and nitrate stress alter the placenta’s function and may cause changes in the fetal programming. Nutrient transfer depends largely on the normal development of the vasculature to allow blood flow and this can be affected by GDM which can cause a decrease in the flow of substrates and is a mechanism in which fetal programming can be affected (Myatt 2006).

Fetal programming involves a large amount of development plasticity and interruptions to this development may cause abnormalities in the development of certain cells which may progress to structural differences in organ development (Gluckman and Hanson 2004 cited in Jansson and Powell 2008 ref 16).

Effects to the fetus exposed to GDM

If a fetus is exposed to a diabetic environment during pregnancy then there can be certain long term effects. These effects can be classified into three groups; Anthropometric, Metabolic or Vascular and Neurological or Psychological. Anthropometric changes are concerned with the rates of growth for both height and weight and in a diabetic environment these can be excessive leading to macrosomia and obesity in later life. Metabolic and vascular changes that occur are abnormal glucose tolerance which can eventually lead to diabetes mellitus. Finally the neurological and psychological changes that can occur are usually minor but development of psychological and intellect can sometimes be deficient (Dabelea and Pettitt 2008).

Potential problems that may arise with the fetus from an exposure to maternal diabetes include abnormal organ mass, altered angiogenesis and increased levels of fetal insulin (Fetita 2006). It has also been found that if there is an increase in weight during pregnancy then there is usually a higher birth weight of the fetus (Humphreys 1954 cited in Catalano 2008 Chapter 11).

The developing fetus cannot synthesise glucose and is dependent on the mother to produce it where it is transported to the fetus via facilitated diffusion through the placenta (Aerts et al 1996 cited in Mello, Parretti and Hod 2008). The result of decreased insulin sensitivity is that there is more glucose available to the developing fetus which can lead to a greater birth weight (Mello, Parretti and Hod 2008).

Using animal models, it has been shown that exposure to high levels of glucose in utero can lead a diminished number of nephrons in the offspring (Amri et al 1999 cited in Fetita 2006 ref 68). This is important as nephrogenesis only occurs in the fetus and stops after birth (Gomez, Norwood 1999). It has been shown that a reduction in the numbers of nephron may affect the rate of progression of renal disease in adults due to an inability to secrete sodium. This may later develop into salt-sensitive hypertension (Brenner et al 1988).

The mechanisms of reduced organ mass, high levels of fetal insulin and defects in angiogenesis may help explain how the fetus programs abnormal glucose tolerance in adulthood as a result of exposure to GDM (Fetita 2006).

Transmission of diabetes from mother to offspring

Exposure to gestational diabetes mellitus increases the risk of the fetus developing abnormal glucose tolerance which may develop into type 2 diabetes. (Fetita et al 2006). The association between greater incidences of the offspring having diabetes with a mother with GDM is greater than what would be predicted that could be passed on by maternal genetics (McLean et al 2006).

One study showed that the phenotype for GDM/T2D was more common in daughters of mothers who were diabetic rather than daughters