Investigating Current Controversies in the Management of Gestational and Pre-gestational Diabetes: Diagnostic Criteria and Neonatal Hypoglycaemia

Shan Jiang

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II. Declarations

Student Declaration:

I declare that the contents of this thesis are of my original work. The use of information from other’s work has been appropriately acknowledged and referenced in this thesis. This thesis has not been submitted for any degree.

I understand that if the candidature is successful, the thesis will be lodged with the Director of University Libraries and be made available for immediate use.

Supervisor Declaration

This thesis has been approved and is ready for submission. This thesis has not exceeded the prescribed word limit.

Student Name: Shan Jiang
Supervisor Name: Ngai Wah Cheung

Signature: ________________________________
Signature: ________________________________

Date: 26/02/2017
Date: 26/02/2017
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- Pregnancy Outcomes in Women with Gestational Diabetes under the Old ADIPS and New IADPSG Diagnostic Criterias. Australian Diabetes Society and the Australian Diabetes Educators Association Annual Scientific Meeting 2015

- Pre-delivery maternal glycaemic control and the risk of neonatal hypoglycaemia in women with pre-gestational diabetes mellitus. Australasian Diabetes in Pregnancy Society Annual Scientific Meeting 2015
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ADIPS - Australasian Diabetes in Pregnancy Society

BGL – blood glucose level

BMI – Body Mass Index

CI – confidence interval

DMIP – diabetes mellitus in pregnancy

GCT – glucose challenge test

GDM – Gestational Diabetes

GLUT4 - glucose transporter 4

HAPO - Hyperglycaemia and Adverse Pregnancy Outcome Study

HOMA-%S - Homeostasis Model Assessment of insulin sensitivity

IADPSG - International Association of Diabetes in Pregnancy Study Groups

ICU – intensive care unit

IL-6 – interleukin 6

IR – insulin receptor

IRS-1 – insulin receptor substrate 1

IV - intravenous

LGA – large for gestation

OGTT – oral glucose tolerance test

OR – odds ratio

PCOS – polycystic ovarian syndrome

SGA – small for gestation

TNF-α – tumour necrosis factor alpha
IX. Abstract

Diabetes mellitus has been associated with an increase in adverse pregnancy outcomes including macrosomia, foetal malformations, premature birth and neonatal hypoglycaemia. Thus, optimizing pregnancy outcomes in women with pre-gestational and gestational diabetes have become an important goal of management. Despite this common goal, in many aspects of the management of pregnancy affected by pre-gestational or gestational diabetes, there is a lack of uniform guideline. This is partly due to the presence of competing evidence or in some instances, an absence of evidence. This thesis aims to examine the evidence from which these controversies arose and provide our own data towards the formulation of uniform guideline.

Two controversial topics surrounding diabetes in pregnancy were explored in this thesis:

1) The Diagnostic Criteria of Gestational Diabetes

The new International Association of the Diabetes and Pregnancy Study Groups (IADPSG) 2010 diagnostic criteria for gestational diabetes (GDM) has been controversial following the recommendations to lower the fasting diagnostic blood glucose level (BGL) to ≥ 5.1, and the inclusion of a 1 hour post 75g oral glucose tolerance test diagnostic BGL of ≥ 10, largely based on the Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) study (1). Issues surrounding the new criteria such as a lack of interventional data to evaluate the effects of treatment, concerns that important risk factors such as obesity were overlooked, and a heavy reliance on the risk derived from a single study have resulted in a non-uniform uptake of the new recommendation by individual institutions and medical organizations.

Thus we conducted a retrospective observational cohort study to compare the pregnancy-related adverse outcomes of women according to the different diagnostic criteria for GDM adjusting for BMI categories. Our study showed that untreated women who would now be diagnosed as GDM under the new IADPSG criteria but not the old Australasian Diabetes in Pregnancy (ADIPS) 1998 GDM criteria were at increased risk of caesarean section and large for gestational age (LGA) infants compared to women without GDM. However, women with obesity have an even higher risk of LGA, caesarean section, with
the additional risk of neonatal shoulder dystocia. On the other hand, women who were previously treated due to diagnosis via the ADIPS 1998 criteria but no longer classified as GDM under the IADPSG 2010 criteria, were found to have increased risk of foetal small for gestation (SGA).

2) Impact of Peripartum Maternal Glycaemic Control and the Risk of Neonatal Hypoglycaemia

There is up to 20 times greater prevalence of neonatal hypoglycaemia in the offspring of mothers with pre-gestational diabetes. The morbidity associated with neonatal hypoglycaemia can range from apnoea to seizures and permanent neurological damage. Hence identifying the modifiable maternal risk factors of neonatal hypoglycaemia are important aspects of prevention and management of this adverse pregnancy outcome. A lack of evidence in this field, particularly examining the relationship between the volatility of peripartum maternal BGL and neonatal glucose at delivery, lends to the controversy on the management of glycaemic control of women with pre-gestational diabetes in labour.

We conducted a retrospective analysis of maternal BGL in labour with their corresponding neonatal BGL at delivery to assess for relationships between maternal and neonatal BGL. Our study demonstrated that the neonatal BGL in the 1st 24 hours of birth is associated with both antenatal and peripartum maternal glycaemic control. We found the risk factors for neonatal hypoglycaemia included higher 3rd trimester maternal HbA1c, maternal smoking, preterm delivery, and foetal LGA. Although there was a negative correlation between the maternal peripartum BGL and trough neonatal delivery BGL, when maternal BGL was controlled within the levels of 4 – 7mmol/L, there was no increased risk of neonatal hypoglycaemia.

Drawing from our study findings, in women with gestational diabetes, we have increased the body of evidence to support the risk imposed by women diagnosed via the new IADPSG 2010 criteria. Yet the increased SGA associated with treatment under the ADIPS1998 criteria calls to attention the need for interventional evidence prior to application of the new diagnostic criteria in order to ensure efficacy and an absence of harm from treatment, while the high risk imposed by obesity highlights a gap in antenatal management to be addressed. From the relationships found between maternal and neonatal BGL in the women with pre-
gestational diabetes, we were able to identify risk factors and formulate an intrapartum glycaemic management guideline aimed to decrease the adverse outcome of neonatal hypoglycaemia. Hence, through these studies, we have provided evidence to resolve some of the controversy surrounding the management of pre-gestational and gestational diabetes in the antepartum and intrapartum period.
1. Thesis Introduction

Diabetes mellitus is a condition of abnormal glucose metabolism commonly associated with chronic macrovascular and microvascular complications. However in the pregnancy period, hyperglycaemia can have profound impacts on both the mother and the foetus, in the short and long term. Prior to the discovery of insulin, both foetal and maternal mortality during pregnancy in those diagnosed with diabetes mellitus was up to 45% (2). In the last 50 years, gestational diabetes has also emerged as a cause of adverse outcomes during pregnancy and beyond.

We now consider there to be 3 major types of diabetes that affect pregnancy, namely

- type 1 diabetes, mainly associated with decreased insulin secretion from beta-islet cells of the pancreas
- type 2 diabetes, mainly associated with increased insulin resistance and relative insulin deficiency
- hyperglycaemia first detected in pregnancy. This is subdivided into gestational diabetes (GDM) defined as carbohydrate intolerance arising during pregnancy, and diabetes mellitus in pregnancy (DMIP). The distinction between the two is based on the diagnostic criteria for diabetes outside of pregnancy (fasting glucose ≥7.1 mmol/L, or 2 hour glucose ≥11.1 mmol/L on the GTT). The separations between GDM, DMIP and type 2 diabetes are somewhat arbitrary, with the cut-off for GDM based on consensus, and the threshold for DMIP based on the diagnostic values for diagnosis of diabetes outside of pregnancy (3). A proportion of women with DMIP may represent pre-existing type 2 diabetes with the only difference being whether it was recognised prior to pregnancy, though up to 41% of women with DMIP can return a normal OGTT result 6 weeks postpartum (4). In practice management of GDM and DMIP is similar, but because women with DMIP are more likely to have pre-existing diabetes and confers a higher risk of adverse pregnancy outcome than women with GDM (4, 5), they should be screened for the presence of diabetes complications, be more rigorously monitored and treated during pregnancy, and have closer follow-up and testing for diabetes post-partum.
Despite significant improvements in treatment decreasing infant mortality in pregnancy affected by pre-existing diabetes to around 2.5%, this is still 3-4 times the rate of those without diabetes (6, 7). The 2005 – 2008 Australian Institute of Health and Welfare report also showed a high incidence of adverse pregnancy outcomes, with up to 5 times increased risk of preterm delivery, 1.5 times the need for induction of labour, almost double the rate of caesarean section, 4 times the risk of hypertension in pregnancy, lower neonatal Apgar scores and double the rate of neonatal resuscitation compared to pregnancies not affected by diabetes. This highlights that our management of diabetes in pregnancy is still suboptimal. It is clear that in some areas, poor pregnancy outcomes relate to the failure to systematically implement best practice, such as pre-pregnancy planning. However, in other areas, what comprises optimal care is unclear, due to lack of data, conflicting research results, or guidelines being formulated by extrapolation of data, rather than through clinical studies. Therefore, a number of controversies exist in the field of diabetes in pregnancy. This thesis seeks to examine 2 such areas, and provide data which may contribute to the development of future best practice guidelines:

i) Whether the new IADPSG diagnostic criteria for GDM are appropriate for an Australian population

ii) The relevance of glucose control immediately before delivery.

Multiple different diagnostic criteria for GDM (8-18) have been formulated since 1964, with some of these also undergoing several updates (8-18). The recent International Association of Diabetes in Pregnancy Study Groups (IADPSG) criteria arose from the desire to develop diagnostic criteria for GDM based on short term and long term neonatal and maternal adverse outcomes associated with hyperglycaemia in pregnancy, and to standardise the criteria internationally. However despite this, four different sets of criteria (16-19) are still in widespread use between Australia, the US and UK in the present day. Although the IADPSG criteria are based on more evidence than previous criteria, the glucose thresholds used are controversial as they were ultimately determined by consensus, and there are no direct data that treatment at these thresholds improves pregnancy outcomes. In this thesis, outcomes of pregnancy with GDM diagnosed under either the old Australasian Diabetes in Pregnancy Society (ADIPS) and new IADPSG criteria will be examined.

Controversy also permeates the literature surrounding the management of diabetes in pregnancy immediately before and during delivery. Due to a paucity of data, particularly with
with respect to neonatal outcome, there is no consensus on the optimal target blood glucose level (BGL) to aim for during this time, and many clinicians just apply by default the targets used during the rest of the antenatal period. Management plans differ across institutions creating inconsistencies in care and sometimes confusion between healthcare professionals. It is therefore important to inject some data relating to peripartum glucose control into the discussion to assist in the development of such management guidelines.

Thus this thesis aims to provide data to shed some light onto some of the important current controversies in the field of diabetes in pregnancy, and evaluate the existing literature surrounding these issues, with particular focus on the diagnostic criteria for GDM and evidence for peripartum glucose management strategies. It is hoped that this will contribute towards the body of evidence which may help resolve some of these controversies.
2. Literature Review

2.1 Gestational Diabetes

2.1.1 Pathophysiology

A series of metabolic adaptations occur during different stages of pregnancy to facilitate the changes in nutrient requirements to the mother and the foetus. At the beginning of pregnancy, insulin secretion increases to promote adipose deposition while insulin resistance is relatively stable. As a result, fasting glucose levels are often lower in women without GDM in early pregnancy. However in the late second trimester, insulin resistance intensifies while insulin clearance rises, to promote formation of circulating free fatty acid and hepatic gluconeogenesis (20). In women without GDM, this decrease in insulin sensitivity with advancing gestation is estimated to be between 47 – 56%, but a functioning homeostatic increase in insulin secretion is sufficient to maintain euglycaemia.

The hormonal environment associated with pregnancy has been proposed as mediators of this insulin resistance. The major hormones involved include human placental lactogen, prolactin, progesterone and cortisol which become elevated in pregnancy and have been shown to induce insulin resistance in adipocyte cultures when present at high concentrations equivalent to that in the 3rd trimester of pregnancy. In in-vitro study, progesterone and cortisol were seen to decrease insulin binding to its cellular receptor and in turn decrease glucose uptake. However prolactin and human placental lactogen did not alter insulin binding yet still resulted in decreased glucose uptake in adipocyte, leading to the speculation that the mechanism of insulin resistance with these hormones are associated with post-binding signalling (21). These findings have been supported by clinical studies. Progesterone was shown to induce insulin resistance in rats as well as in post-menopausal women on progesterone containing hormone replacement therapy (22, 23). Cortisol excess in Cushings disease is well known to result in hyperglycaemia. The Homeostasis Model Assessment of insulin sensitivity (HOMA-%S) was found to be lower in states of hyperprolactinaemia (24). The antagonistic action of human placental lactogen to insulin has been demonstrated in infusion study in human subjects (25). On the other hand, the other major hormone in
pregnancy, oestradiol, was found to increase insulin binding leading to increased insulin sensitivity, yet this action is likely to be overwhelmed by action of other hormones that promote insulin resistance.

Gestational diabetes is a state of carbohydrate intolerance first recognized during pregnancy (26). In women with GDM, using the hyperinsulinaemic-euglycaemic clamp study, it was found that there was a heightened second phase insulin response compared to control women without GDM, however there was less resultant suppression of hepatic gluconeogenesis(27). This suggests that in women with GDM despite an absolute increase in insulin secretion, the insulin resistance occurring is disproportionately higher than the amount of insulin secreted in order to achieve glycaemic equilibrium. The inability for further increase insulin secretion to overcome the insulin resistance also hints at the possibility of a suboptimal beta-islet cell function.

Cytokines and adipokines have also been postulated to induce insulin resistance in GDM. An increase in tumour necrosis factor alpha (TNF-α) release from the placenta has been shown to occur in the later part of pregnancy. The amount of circulating TNF-α and insulin sensitivity were observed to be inversely correlated. From in vitro studies, it has been shown that TNF-α has the ability to downregulate insulin receptor signalling via impeding the autophosphorylation of the insulin receptor. (20) Interleuken-6 (IL-6), a pro-inflammatory cytokine with a possible role in insulin resistance and derived partially from adipocytes, has been found to be increased in states of insulin resistance including GDM (28). However it is unclear whether these pro-inflammatory cytokines in states of increased adiposity such as pregnancy and obesity are directly inducing the hyperglycaemia in GDM, or rather, the hyperglycaemia itself triggering a pro-inflammatory state promoting these cytokines leading to a vicious cycle of insulin resistance. The anti-inflammatory cytokine Adiponectin, which has many actions complementary to insulin, has been shown to be decreased in women with GDM and other insulin resistant states, while the level and role of leptin in GDM has been less consistently implicated in the pathogenesis of insulin resistance in GDM (28, 29).

Defects in various cellular processes involved in insulin action in GDM women have been proposed to explain the increased insulin resistance in GDM women (30). The binding of insulin to the insulin receptor (IR) induces auto-phosphorylation of the receptor β-subunit to activate insulin receptor tyrosine kinase that acts to phosphorylate various downstream substrates including insulin receptor substrate 1 (IRS-1). This process in turn activates the
phosphatidyl-inositol-3-kinase enzyme to produce further intracellular signalling cascade that serves to mediate insulin actions such as translocation of the glucose transporter 4 (GLUT4) to the cell surface for uptake of glucose. This process is modulated by inhibitory enzymes such as glycoprotein-1 and serine/threonine kinase to halt the signalling cascade (20). In women with GDM, the phosphorylation process of the insulin receptor has been shown to be decreased compared to women without GDM, thus dampening the effect of insulin transduction. In addition, there appears to be an excess of serine phosphorylation by serine kinase which serves to inactivate the insulin signalling. Further downstream, the IRS-1 protein which regulates the glucose uptake has been shown to be reduced by 30 – 50% in skeletal tissue of women with GDM and obese pregnant women. The IRS-1 signalling is also impeded by the serine kinase action thus further preventing the execution of insulin action. Moreover, the downregulation of GLUT4 transporter in adipose tissue which occurs in normal pregnant women is more exaggerated in women with GDM. These multi-levels of impaired insulin action signalling not only highlights the complexity of the condition, but also serves to show potential future treatment targets.

2.1.2 Risk Factors

Several risk factors are associated with the development of gestational diabetes. Knowledge regarding risk factors is important as it allows identification of potential modifiable factors for prevention, management, efficient targeting of the at risk populations for education, and possibly screening and early diagnosis. Multiple studies have consistently demonstrated advanced maternal age, non-Caucasian ethnicities, obesity, increased gestational weight, and family history of diabetes to be risk factors associated with the development of GDM (31-34). The inherent insulin resistance associated with Polycystic Ovarian Syndrome (PCOS) also confers more than double the risk of GDM(35). One large prospective study of 14613 women also found that pre-gravid smoking to be a risk factor with a relative risk of 1.43 (34). This presence of both modifiable and non-modifiable risk factors reinforces the disease model of GDM as a condition having a genetic predisposition with environmental influences. Having had GDM in a previous pregnancy confers a 35.6 – 70% risk of having GDM in future pregnancy (36, 37). The characteristics of the women who are at higher risk of recurrence have been explored. Maternal obesity, previous GDM, need for insulin in previous GDM pregnancy, increased weight gain between pregnancies, increased maternal age, non-
Caucasian ethnicity and greater glucose levels on oral glucose tolerance test (OGTT) have been shown to be common factors in women with recurrent GDM (36, 38). It can be seen that there is significant overlap in risk factors between the initial development of GDM and its subsequent recurrence, hence it may be speculated that treating overlapping modifiable risk factors may have the potential to decrease the onset of GDM and its recurrence.

Ethnicity has been consistently been found to be a major independent risk factor of development and recurrence of GDM (31). Based on one systematic review of 13 studies, ethnicity was found to be the single most significant risk factor consistently demonstrated across studies for the recurrence of GDM (39). Apart from the non-Hispanic white ethnic group, other ethnic minorities such as African Americans, Latinas, Asians, all exhibited GDM recurrence rate of >50% in the studies included in the analysis. In Australia, a study of an ethnically diverse population has shown that South Asians and East Asians have 3 – 5 times the risk of GDM compared to Caucasian women (40). Moreover, women with gestational diabetes differ in clinical characteristics in terms of their 75g OGTT results, offspring birthweight, and likelihood to require insulin therapy based on their ethnicity (41). In addition, rather than ethnicity delineated by country, the indigenous population within the country appear to be at increased risk of GDM. An age adjusted comparison of 25 Australian studies have shown Australian Aboriginal women had higher risk of GDM than their non-indigenous counterparts (42). This is in accordance with international indigenous data where one meta-analysis of 42 studies found that 65% of the studies reported higher GDM prevalence in the indigenous populations such as the Pacific Islanders, Canadian Aboriginals, American Indians and Australian Aboriginals compared to non-indigenous groups (43).

Studies exploring the pathogenesis of the increased risk have found that not only do East Asians and South Asians have greater insulin resistance than Caucasians during pregnancy, there is also evidence of poorer beta-cell function and thus failure to compensate for the insulin resistance leading to carbohydrate intolerance (44, 45). Examining the environmental factors, the altered western diet and lifestyle in the ethnic migrant population has been considered a possible contributor to the propensity for GDM (46), whereas cultural perceptions in the harms of diet and exercise in pregnancy in South Asian women have been found to be barriers to adherence to lifestyle interventions (47). Therefore, it appears that the ethnic migrant population is a group at high risk of GDM and its recurrence that may require a tailored culturally-appropriate approach to gain successful intervention.
The presence of risk factors for GDM has clinical, diagnostic and interventional implications for the women. One of the clinical impacts of having a risk factor for GDM in the past was that it prompted the women to have screening test of either a 50g glucose challenge test (GCT) or the diagnostic 75g OGTT during pregnancy, whereas those without risk factors were not necessarily screened for GDM. However there has been controversy regarding the sensitivity of this approach. There have been competing studies with some showing that risk factor screening did not significantly reduce sensitivity while greatly increasing the positive predictive ratio, leading to health resource savings (48, 49). However other studies have yielded results showing selective screening in women with risk factors could potentially lead to 43% of missed diagnosis (50, 51). Part of the discrepancy in the result could be due to the differences in diagnostic criteria, the population studied, and risk factors used in the screening procedure between the studies. This lack of reliability in risk factor only screening has led to its abandonment in the recent recommendations by both the ADIPS and IADPSG, which now both endorse universal testing with an OGTT in pregnancy but with earlier testing in those with risk factors. The ADIPS 2014 recommendation lists previous hyperglycaemia in pregnancy, previous elevated BGL, maternal age ≥40 years, ethnicity from Asian, Indian subcontinent, Aboriginal, Torres Strait Island, Pacific Islander, Maori, Middle Eastern, non-white African, family history of DM, pre-pregnancy BMI >30kg/m², previous macrosomia, polycystic ovarian syndrome, medication use such as corticosteroid or antipsychotic, as suggested risk factors for early OGTT prior to 2nd trimester to diagnose GDM (52).

Given the modifiable risk factors mentioned, several studies have examined whether intervention in these risk factors would decrease the onset and recurrence of GDM. In women with PCOS, there is some evidence of metformin use in reducing the development of GDM, albeit the study sample in these studies were small (53, 54). In one prospective observational study there appeared to be no association between increasing pre-gravid physical exercise with reduction in development of GDM (34). Cochrane systematic analyses on dietary interventions and exercise have both yielded inconclusive results for prevention of GDM (55, 56). One systematic review (57) examining 19 randomised control trials on intervention via either metformin therapy, low glycaemic index diet, dietary counselling, probiotic use, self-monitoring of weight gain, and exercise found that only dietary counselling yielded a reduction in GDM development. Although there was also significant reduction in GDM in the probiotic use study, this was only a single small study hence definitive conclusions could not be drawn. Hence currently, there are some evidence to suggest that certain risk factor
modification may prevent GDM. However, a common theme emphasized in these systematic reviews on prevention of GDM was the lack of large sample size high quality trials, and this would be an important future research direction to undertake to further solidify evidence.

2.1.3 GDM Diagnostic Criteria

The diagnostic criteria for gestational diabetes (GDM) has evolved through the decades, though only in part based on our increased understanding of the risks associated with this state of carbohydrate intolerance first recognized during pregnancy(58). Otherwise many of the criteria were based on consensus, statistical distributions, and extrapolations from diabetes in general. Table 1 shows some of the major diagnostic criteria recommended since 1964.
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<tr>
<th>Diagnostic Criteria</th>
<th>Screening test</th>
<th>OGGT glucose dose</th>
<th>Fasting BGL</th>
<th>1hr BGL</th>
<th>2hr BGL</th>
<th>3hr BGL</th>
<th>Diagnostic Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>O’Sullivan 1964(8)</td>
<td>100g</td>
<td>5.3mmol/L (5.0mmol/L)</td>
<td>10.0mmol/L (9.2mmol/L)</td>
<td>8.7mmol/L (8.1mmol/L)</td>
<td>7.7mmol/L (6.9mmol/L)</td>
<td>2 or more positive values</td>
<td></td>
</tr>
<tr>
<td>O’Sullivan 1973(9)</td>
<td>50g GCT, 1hr BGL≥7.3mmol/L (7.2mmol/L)</td>
<td>100g</td>
<td>5.3mmol/L (5.0mmol/L)</td>
<td>10.0mmol/L (9.2mmol/L)</td>
<td>8.7mmol/L (8.1mmol/L)</td>
<td>7.7mmol/L (6.9mmol/L)</td>
<td>Screen with 50g GCT, if 1hr BGL≥7.9mmol/L then progress to 100g OGGT with diagnosis based on 2 or more positive values.</td>
</tr>
<tr>
<td>Carpenter and Coustan 1982(10)</td>
<td>50g GCT, 1hr BGL≥7.3mmol/L (7.2mmol/L)</td>
<td>100g</td>
<td>5.3mmol/L (5.0mmol/L)</td>
<td>10.0mmol/L (9.2mmol/L)</td>
<td>8.6mmol/L</td>
<td>7.8mmol/L</td>
<td>Screen with 50g GCT, if 1hr BGL≥7.5mmol/L then progress to 100g OGGT with diagnosis based on 2 or more positive values.</td>
</tr>
<tr>
<td>World Health Organization 1985(26)</td>
<td>75g</td>
<td>7.8mmol/L</td>
<td>11.1mmol/L</td>
<td>If symptomatic, then only need random BGL≥11.1mmol/L. If asymptomatic, need a positive random BGL and a OGTT positive at both fasting and 2hr.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mercy Hospital 1986(11)</td>
<td>50g</td>
<td>9mmol/L</td>
<td>7.0mmol/L</td>
<td>Need both results positive for diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Australian Diabetes Society and Australasian Diabetes in Pregnancy Society 1991(12), 1998(18)</td>
<td>Either 50g or 75g GCT, 1hr BGL≥7.8mmol/L for 50g load, 1hr BGL≥8.0mmol/L for 75g load</td>
<td>75g</td>
<td>5.5mmol/L</td>
<td>8.0mmol/L</td>
<td>Need one result positive for diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sacks 1995(59)</td>
<td>75g</td>
<td>5.6mmol/L</td>
<td>10.8mmol/L</td>
<td>8.9mmol/L</td>
<td>2 values positive for diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>American Diabetes Association 1997(15)</td>
<td>50g GCT, 1hr BGL≥7.8mmol/L</td>
<td>75g</td>
<td>5.3mmol/L</td>
<td>10.0mmol/L</td>
<td>8.6mmol/L</td>
<td>2 values positive for diagnosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>100g</td>
<td>5.3mmol/L</td>
<td>10.0mmol/L</td>
<td>8.6mmol/L</td>
<td>7.8mmol/L</td>
<td>diagnosis based on 2 or more positive values.</td>
<td></td>
</tr>
<tr>
<td>World Health Organization 1998(14)</td>
<td>75g</td>
<td>7.0mmol/L</td>
<td>7.8mmol/L</td>
<td>BGL satisfying fasting or 2 hour BGL thresholds.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>International Association of Diabetes in Pregnancy Study Group 2010(16)</td>
<td>75g</td>
<td>5.1mmol/L</td>
<td>10.0mmol/L</td>
<td>8.5mmol/L</td>
<td>One value positive for diagnosis.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>National Institute of Health and Care Excellence 2015(17)</td>
<td>75g</td>
<td>5.6mmol/L</td>
<td>7.8mmol/L</td>
<td>One value positive for diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*All non-bracketed BGL levels are venous plasma BGL levels.*  
*Bracketed BGL levels are whole blood levels derived by the Somogyi-Nelson method.*  
*Please see Table 3 for current diagnostic criterias adopted by expert bodies.*
The first widely accepted diagnostic criteria were formulated in 1964, based on the subsequent maternal risk of postpartum type 2 diabetes\textsuperscript{(8)}. These criteria were derived from the statistical distribution of the oral glucose tolerance test of 752 normal pregnant women, then validated on 1013 pregnant women to assess the risk of developing type 2 diabetes within the 8 years postnatally. The resulting criteria reached corresponded to 100g O\textsubscript{GTT} values approximately 2 standard deviations above the mean based on whole blood glucose levels derived by the Somogyi-Nelson method. The fasting threshold was set at 5.0mmol/L, 1hour threshold at 9.2mmol/L, 2hour threshold at 8.1mmol/L and 3hour threshold at 6.9mmol/L. Two or more values were needed for diagnosis in order to avoid false positives due to laboratory error or unusual rapid absorption of glucose causing transient single peak in blood glucose. These criteria had a positive predictive value of 22.6% for the subsequent development of type 2 diabetes, and a prevalence of 1.99%. However the OGTTs were performed in different trimesters, with more than half of the OGTT results obtained in the 1\textsuperscript{st} and 2\textsuperscript{nd} trimester, and half obtained in the 3\textsuperscript{rd} trimester. Hence it is difficult to determine the applicability of this OGTT data given the change in insulin resistance with increasing trimesters that we now know would affect the OGTT result. In this very first diagnostic criteria, it was recognized that the diagnostic criteria was derived from a risk that was continuous without a clear threshold and the clinical significance was not based on pregnancy outcomes.

In 1973, O’Sullivan et al introduced the 50g GCT as a screening procedure which alleviated the need for a universal OGTT\textsuperscript{(9)}. A 50g glucose was introduced whereby only those obtaining a positive result of BGL$\geq$7.9mmol/L 1 hour post ingestion of the glucose load would proceed to having a formal OGTT. This screening test achieved a sensitivity of 79% and a specificity of 87% for the subsequent diagnosis of GDM on the 75g OGTT. This screening test was further refined by Carpenter and Coustan in 1982 whereby the sensitivity reached greater than 90% with minimal compromise of the specificity at 80% achieved by lowering the 50g GCT threshold to 135mg/dL (7.5mmol/L)\textsuperscript{(10)}. They also recommended the timing of the diagnostic test to be performed between 24 – 33 weeks gestation, converted the whole blood glucose levels obtained via the Somogyi-Nelson method into the venous plasma levels and rounded the figures to the nearest 5 mg/dl. These diagnostic and screening criteria so far did not incorporate into their formulation the risk of immediate adverse pregnancy outcomes that were emerging\textsuperscript{(60)} to become the focus of the diagnostic criteria for gestational diabetes of the present day.
Although the US more readily adopted the Carpenter and Coustan screening test and the O’Sullivan threshold for OGGTT for diagnosis of gestational diabetes, these criteria were less accepted worldwide. In 1985, the World Health Organization (WHO) had recommended the use of the diagnostic criteria for type 2 diabetes for diagnosis of gestational diabetes (26). This was revised in 1998 to incorporate both the diagnostic criteria for type 2 diabetes and impaired glucose tolerance at 24 to 28 weeks gestation to be classified as gestational diabetes which was originally devised based on the risk of microvascular disease (14). This reflected the lack of high level evidence at the time in determining the risks of gestational diabetes.

Given the differences in the dose of glucose for the OGGTT and threshold level of diagnosis, there was a drive towards the development of a uniform diagnostic criteria for GDM that incorporated the risk of adverse pregnancy outcomes. Sacks et al in 1995 formulated a 75g OGGTT criteria for the diagnosis of GDM based on the statistical distribution of OGGTT values in 3505 women and the risk of neonatal macrosomia (59). The testing was recommended to be performed in 24 – 28 gestation in order for timely intervention to occur in the third trimester. Like the dilemma posed to O’Sullivan, the study showed a positive linear relationship between maternal hyperglycaemia and macrosomia, with no clear threshold for increased risk, and therefore the same statistical approach of setting a cut off at 2 standard deviations above the mean was applied, arriving at an incidence of GDM of 3.2% and statistical significance in the risk of macrosomia in the diagnostic group. In 1997, the American Diabetes Association recognized both the traditionally used 100g OGGTT Carpenter and Coustan diagnostic criteria which had been used for more than a decade and the 75g OGGTT study from Sacks et al, albeit with modifications on both in order to consolidate the criteria (15). Screening was no longer recommended to be universal but only in those with risk factors. The 50g GCT threshold was raised to 140mg/dL (7.8 mmol/L) to improve the specificity. The 75g OGGTT threshold values were based on levels 1.5 standard deviations above the mean with a raised 2hour level to reach consistency with the 100g OGGTT. Despite the fusion of the competing diagnostic criteria at the time, it nevertheless remained 2 separate tests, a temporary measure until a single unifying diagnostic criteria is created.

Within Australia, the various diagnostic criteria used have been based on both local and international data. One of the earliest diagnostic criteria developed locally at the Melbourne Mercy Hospital in 1985 was a 50g OGGTT which was based on the analysis of 18679 women and their risk of perinatal outcomes of stillbirth, neonatal deaths, foetal growth retardation and congenital anomalies (11). Although this was one of the first diagnostic criteria
developed based on perinatal risk, it was not very widely used throughout Australia. The need for a unifying diagnostic criteria within Australian was recognized with a publication by the Australian Diabetes Society in 1991 (12) and the Australasian Diabetes in Pregnancy Society in 1998(18), recommending the use of either a 50g or 75g GCT for screening, and a 75g OGTT diagnostic test derived from the statistical distribution of maternal blood glucose level in pregnancy of European and Australian women, as well as rounding off of the WHO diagnostic criteria (12). Screening was recommended for all pregnant women to occur at 26 – 28 weeks gestation consistent with international recommendations. Promotion of this diagnostic criteria through these publications allowed for a locally standardized diagnosis for gestational diabetes within Australia.

2.1.3a The Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) Study

The lack of large studies investigating the correlation of maternal hyperglycaemia and the risk of adverse pregnancy outcome was a shortcoming which led to the HAPO study. Published in 2008(1), this became the landmark study redirecting the focus of gestational diabetes criteria from prediction of long term maternal development of type 2 diabetes towards the more immediate adverse effects of maternal hyperglycaemia on the outcomes of pregnancy. This was a prospective blinded observational study of 23316 patients from 15 centres in 9 different countries examining the relationship between the maternal 75g OGTT undertaken at 24 – 32 weeks gestation and the risk of developing the adverse primary outcomes of large for gestation (LGA) >90th percentile of gestational age, primary caesarean section, neonatal hypoglycaemia, high cord c-peptide above the 90th percentile, and secondary outcomes of preterm delivery <37 weeks gestation, shoulder dystocia or birth injury, need for neonatal intensive care, hyperbilirubinaemia and pre-eclampsia. The odds ratio (OR) of the adverse pregnancy outcome was calculated for each aspect of the 75g OGTT of fasting, 1 hour and 2 hour maternal BGL. The odds ratios were based on comparison with the lowest of 7 categories of the OGTT levels, whereby the fasting was \(\leq 75\text{mg/dL (4.2mmol/L)}\), 1hr BGL\(\leq 105\text{mg/dL (5.8mmol/L)}\), and 2hr BGL\(\leq 90\text{mg/dL (5.0mmol/L)}\).

In addition, the study presented multivariate models adjusting for multiple confounders to improve the validity of the study in determining independent relationships between maternal
OGTT values and the risk of adverse pregnancy outcomes. The results of the study found that there was a strong positive association between all 3 glucose components of the OGTT to the four primary outcomes of neonatal LGA, cord c-peptide, primary caesarean section and neonatal hypoglycaemia (see figure 1). Moreover, there was also a positive association between the maternal glucose level on OGTT in relation to preterm delivery, shoulder dystocia or birth injury, intensive neonatal care, hyperbilirubinaemia and pre-eclampsia. These results paved the way for the formulation of the most recent diagnostic criteria as defined by the International Association of Diabetes in Pregnancy Study Group (IADPSG).
Figure 1: Frequency of Primary Outcomes Across the Glucose Categories in the HAPO Study

**Figure 1. Frequency of Primary Outcomes across the Glucose Categories.**

Glucose categories are defined as follows: fasting plasma glucose level — category 1, less than 75 mg per deciliter (4.2 mmol per liter); category 2, 75 to 79 mg per deciliter (4.2 to 4.4 mmol per liter); category 3, 80 to 84 mg per deciliter (4.5 to 4.7 mmol per liter); category 4, 85 to 89 mg per deciliter (4.8 to 4.9 mmol per liter); category 5, 90 to 94 mg per deciliter (5.0 to 5.2 mmol per liter); category 6, 95 to 99 mg per deciliter (5.3 to 5.5 mmol per liter); and category 7, 100 mg per deciliter (5.6 mmol per liter) or more; 1 hour plasma glucose level — category 1, 105 mg per deciliter (5.8 mmol per liter) or less; category 2, 106 to 132 mg per deciliter (5.9 to 7.3 mmol per liter); category 3, 133 to 155 mg per deciliter (7.4 to 8.6 mmol per liter); category 4, 156 to 171 mg per deciliter (8.7 to 9.5 mmol per liter); category 5, 172 to 193 mg per deciliter (9.6 to 10.7 mmol per liter); category 6, 194 to 211 mg per deciliter (10.8 to 11.7 mmol per liter); and category 7, 212 mg per deciliter (11.8 mmol per liter) or more; and 2 hour plasma glucose level — category 1, 90 mg per deciliter (5.0 mmol per liter) or less; category 2, 91 to 108 mg per deciliter (5.1 to 6.0 mmol per liter); category 3, 109 to 125 mg per deciliter (6.1 to 6.9 mmol per liter); category 4, 126 to 139 mg per deciliter (7.0 to 7.7 mmol per liter); category 5, 140 to 157 mg per deciliter (7.8 to 8.7 mmol per liter); category 6, 158 to 177 mg per deciliter (8.8 to 9.8 mmol per liter); and category 7, 178 mg per deciliter (9.9 mmol per liter) or more.

Figure taken from and reproduced with permission from Hyperglycemia and Adverse Pregnancy Outcomes. *New England Journal of Medicine.* 2008; 358: 1991-2002. Copyright Massachusetts Medical Society
2.1.3b The IADPSG diagnostic criteria for gestational diabetes

The finding that maternal hyperglycaemia below that of the overt diabetes range is independently associated with adverse pregnancy outcomes in the HAPO study was the basis under which the IADPSG formulated the new diagnostic criteria (16). Universal 75g glucose tolerance testing in all pregnant women was recommended at 24 – 28 weeks gestation, with some form of early testing as well in those at high risk. The diagnostic thresholds were fasting BGL≥5.1mmol/L, 1 hour BGL≥10.0mmol/L, 2 hour BGL≥8.5mmol/L. Only one level above the threshold is required for diagnosis of GDM. The diagnostic yield of the fasting, 1hour and 2hour BGL are shown in Table 2.

Table 2: Diagnostic Yield of the IADPSG GDM Diagnostic Criteria Glucose Measures.

<table>
<thead>
<tr>
<th>Glucose Measure</th>
<th>BGL threshold</th>
<th>Cumulative % of HAPO study population above threshold (16)</th>
<th>Cumulative% of HAPO GDM population above threshold (61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting BGL</td>
<td>≥5.1mmol/L</td>
<td>8.3</td>
<td>55%</td>
</tr>
<tr>
<td>1hr BGL</td>
<td>≥10.0mmol/L</td>
<td>14.0</td>
<td>88%</td>
</tr>
<tr>
<td>2hr BGL</td>
<td>≥8.5mmol/L</td>
<td>16.1</td>
<td>100%</td>
</tr>
</tbody>
</table>

The consistency of the HAPO study results across the centres involved in the study, cemented its validity as a foundation to base the new diagnostic criteria. When reanalysing the HAPO data with these thresholds, it was also found that these OGTT levels were also predictive of an increased risk of pre-eclampsia and shoulder dystocia. However a major issue in devising the new diagnostic criteria was the fact that the risks associated with maternal hyperglycaemia was continuously linear without a clear threshold. Thus the IADPSG panel determined by consensus, that the 75g OGTT values which confer an average odds ratio of 1.75 compared to the study population OGTT mean values in the four major adverse pregnancy outcome domains of LGA, high cord c-peptide, primary caesarean section and neonatal hypoglycaemia, be used as the threshold for the new diagnostic criteria for GDM. An alternative odds ratio of 2.0 was considered, however the cumulative percentage of the population diagnosed decreased from 16.1% to 8.8% which would exclude a substantial number of women who are at similar risk of adverse pregnancy outcomes yet would be excluded from treatment due to just falling short of the diagnostic criteria (16). Therefore,
amongst the diagnostic criteria thus far, the IADPSG 2010 diagnostic criteria is the one that has encompassed the most clinically relevant evidence of perinatal outcome into its conception.

2.1.3c Controversies related to the IADPSG diagnostic criteria

Although the IADPSG 2010 diagnostic criteria has now gained recognition and recommendation by organizations such as the WHO and ADIPS, it has not gained universal acceptance. Table 3 gives an overview of the major international organizations that have and have not adopted the IADPSG criteria by the end of 2016.

Table 3: Adoption of the IADPSG Criteria by Countries

<table>
<thead>
<tr>
<th>Organizations Utilizing the IADPSG Criteria</th>
<th>Organizations Not Utilizing the IADPSG Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO</td>
<td>NIH</td>
</tr>
<tr>
<td>ADIPS (Australia)</td>
<td>American College of Obstetricians and Gynecologists</td>
</tr>
<tr>
<td>American Diabetes Association</td>
<td>UK NICE</td>
</tr>
<tr>
<td>Australian Diabetes Society</td>
<td>European Association for the Study of Diabetes</td>
</tr>
<tr>
<td>RANZCOG</td>
<td>Diabetes in Pregnancy Study Group India</td>
</tr>
<tr>
<td>IADPSG</td>
<td>New Zealand</td>
</tr>
<tr>
<td>Royal College of Pathologists of Australasia</td>
<td></td>
</tr>
<tr>
<td>SOMANZ</td>
<td>RACGP</td>
</tr>
<tr>
<td>International Federation of Gynecology and Obstetrics</td>
<td></td>
</tr>
<tr>
<td>Canadian Diabetes Association</td>
<td></td>
</tr>
<tr>
<td>Chinese Diabetes Association</td>
<td></td>
</tr>
<tr>
<td>Japanese Diabetes Association</td>
<td></td>
</tr>
<tr>
<td>Brazil</td>
<td></td>
</tr>
<tr>
<td>Italy</td>
<td></td>
</tr>
<tr>
<td>Greece</td>
<td></td>
</tr>
<tr>
<td>Germany</td>
<td></td>
</tr>
<tr>
<td>Austria</td>
<td></td>
</tr>
</tbody>
</table>
One of the major concerns is the use of the observational HAPO study as the major basis for the formulation of the IADPSG 2010 diagnostic criteria whereby the cut-offs were based on arbitrary value determined by consensus. Even though the WHO has adopted the new diagnostic criteria, it is still classified as based on weak evidence due to this lack of interventional data(62). In addition, there are discordant results from the various retrospective studies comparing the risk of untreated women with GDM versus those without GDM. Sacks et al(63) compared 9835 untreated women who fell below the institutional diagnostic criteria for GDM and divided them into 3 cohorts consisting of those without GDM, those diagnosed via the IADPSG 2010 criteria via the lower and higher ranges of the IADPSG diagnostic criteria. When compared to women without GDM, it was found that women meeting the higher ranges of the diagnostic criteria were indeed at increased risk of pre-eclampsia, preterm delivery, primary caesarean section, shoulder dystocia, higher birth weight, ponderal index, LGA, transient tachypnoea and neonatal hypoglycaemia compared to no GDM. However women who met the lower ranges of the IADPSG diagnostic criteria were only at higher risk of increased birth weight and LGA without the risk of other adverse pregnancy outcomes, thus questioning the value of the diagnostic criteria. Another study comparing the Canadian Diabetes Association criteria with the IADPSG criteria showed no significant difference in perinatal outcomes of LGA, preterm birth, pre-eclampsia and delivery complications between the ‘Canadian criteria negative IADPSG positive’ group and the no GDM group (64). Limitations of this study included the fact that the Canadian criteria was already very similar to the IADPSG criteria, while other critics have commented on the inadequate power of the study (65).

On the other hand, there are also studies which support the benefits of applying the IADPSG criteria. A large British study consisting of 25543 women compared the perinatal outcomes between non-GDM, treated women with GDM via the NICE 2015 guideline and untreated women diagnosed via IADPSG 2010 criteria, found that those under the IADPSG criteria had significant risk of LGA, caesarean section including emergency caesarean section, and polyhydramnios, whilst women with higher fasting BGL had the highest risk of LGA (66). Other studies have also demonstrated a plethora of increased risks including LGA, hypertensive disease, and caesarean delivery associated with the untreated GDM based on the IADPSG 2010 criteria, which would support the new criteria (67-69). Table 4 includes a list of studies comparing adverse pregnancy outcomes between mother without GDM and mothers with IADPSG 2010 GDM which falls outside an established diagnostic criteria.
From most of these studies, it appears that LGA is a consistent complication related to women satisfying the IADPSG criteria, the next step is to assess whether interventions in those identified to be at risk could improve the outcome.

Table 4: Studies comparing the risk of adverse perinatal outcome of women diagnosed with GDM via the IADPSG2010 diagnostic criteria outside of established institutional criteria with non-GDM women.

<table>
<thead>
<tr>
<th>Study</th>
<th>Established diagnostic criteria</th>
<th>Adverse Perinatal Outcome amongst women diagnosed by IADPSG criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lapolla et al 2011(68)</td>
<td>4th International Workshop-Conference on Gestational Diabetes(70)</td>
<td>Increased risk with IADPSG2010 criteria</td>
</tr>
<tr>
<td>Bodmer-Roy et al 2012(64)</td>
<td>Canadian Association 2008</td>
<td>Similar risk to non-GDM</td>
</tr>
<tr>
<td>Ethridge et al 2014(71)</td>
<td>Carpenter-Coustan</td>
<td>Increased risk with IADPSG2010 criteria</td>
</tr>
<tr>
<td>Mayo et al 2015(69)</td>
<td>Canadian Association 2008</td>
<td>Similar risk to non-GDM</td>
</tr>
<tr>
<td>Meek et al 2015(66)</td>
<td>NICE 2015</td>
<td>Increased risk with IADPSG2010 criteria</td>
</tr>
<tr>
<td>Pan et al 2015(67)</td>
<td>1999 WHO criteria</td>
<td>Increased risk with IADPSG2010 criteria</td>
</tr>
<tr>
<td>Sacks et al 2015(63)</td>
<td>Canadian Diabetes Association 2013</td>
<td>Increased risk with IADPSG2010 criteria</td>
</tr>
<tr>
<td>Laafira et al 2016(72)</td>
<td>ADIPS1998</td>
<td>Increased risk with IADPSG2010 criteria</td>
</tr>
</tbody>
</table>

Another major cause of reluctance to utilize the IADPSG 2010 criteria is the lack of intervention data demonstrating consistent improvement of outcomes in treating those with GDM diagnosed under the new criteria. The existing interventional trials(73, 74) showing benefit of treating GDM were not conducted using the IADPSG criteria hence may not necessarily apply to the milder end of the spectrum of this population. The limited prospective observational studies available(75, 76) have shown a decrease in adverse perinatal outcomes associated with treating women with GDM diagnosed via the IADPSG criteria when compared with the perinatal outcomes when a previous GDM criteria was applied. In particularly some studies have found no significant increase in adverse outcomes of LGA or pregnancy-associated hypertensive disease, which had previously been associated
with women with IADPSG GDM (77, 78). Currently there are no randomised control trials to address this issue.

The clinical significance of incorporating the risk for high cord c-peptide has also been questioned as there is no clinical evidence to link high cord c-peptide with clinical adverse outcomes (79). Thus its inclusion as one of the 4 major determinants of adverse pregnancy outcomes used in formulation of the IADPSG 2010 diagnostic criteria is of doubtful relevance, and its subsequent contribution towards the combined odds ratio of 1.75 resulting in a lowering of the diagnostic BGL values threatens the clinical validity of the diagnostic criteria (79, 80).

Critics of the IADPSG 2010 criteria have also expressed concerns regarding issues with the new diagnostic criteria’s high dependency on the accuracy of a single measurement. The lack of data showing the increase in odds ratio of individual adverse pregnancy outcomes occurring based on single OGTT BGL values calls to question the validity of using single values for diagnosis of GDM (79, 80). Moreover, by basing the diagnosis on a single abnormal blood glucose level, there is a risk of high false positives given the inconsistency of the OGTT itself, leading to unnecessary intervention in the mother resulting in extra maternal stress and wasted health cost (81).

The elimination of the 50g GCT from the previous 2 staged diagnosis onto universal screening via 75g OGTT has also been under scrutiny. From an analysis of the original HAPO population, 78% of LGA occurred in women who were below the IADPSG diagnostic criteria, hence without GDM, while in the women who did have GDM, BMI contributed more towards the risk of LGA than hyperglycaemia except in the highest glucose category (82). Moreover, there is a lack of interventional trial to show that treating those diagnosed via universal diagnosis method yields better pregnancy outcome compared to those diagnosed via the 2 step method. Therefore the use of a universal 75g OGTT may increase the incidence of GDM without necessarily increase the identification of women at risk of adverse pregnancy outcomes such as LGA. This opinion has been further supported by observational studies comparing the universal IADPSG diagnostic criteria with the two step Carpenter-Coustan method (83, 84) which showed no difference in adverse pregnancy outcomes, in particularly LGA, in those treated via the IADPSG2010 diagnosis versus the Carpenter-Coustan criteria. Instead, universal screening not only increased the proportion of women diagnosed with GDM but was also associated with increased caesarean section and neonatal ICU admission. However these retrospective observational studies all suffer from 2 limitations. Firstly being
the change in other obstetric practice over time which may have altered pregnancy outcome and thus confounding the effect of change in diagnostic criteria. Secondly, by only comparing the pregnancy outcomes of those treated for GDM, the study design does not allow valid comparison of the risk associated with the 2 diagnostic criteria, as those who would be diagnosed via the alternative criteria but untreated were not included in the studies. Without concrete evidence that treating the new IADPSG 2010 diagnosed GDM population yields benefit over existing practice and the concern regarding the overtreatment, excess investigations, health spending and patient anxiety that may be associated with the increased incidence of diagnosis, organizations such as the American College of Obstetrics and Gynaecology have resisted the change to a one step universal diagnostic method.

Further potential impact of changing to the IADPSG 2010 diagnostic criteria include the increase in incidence of women labelled as having gestational diabetes and its subsequent strain it may have on the health system. Most studies have reported an increase in prevalence associated with diagnosis via the IADPSG criteria, including studies conducted in an Australian population which report up to a one third increase in prevalence from a baseline of 7.9 – 9.6% via the ADIPS 1998 diagnostic criteria, to 8.9 – 13% via the IADPSG 2010 criteria (85, 86). Flack et al (87) conducted an estimation of the change in workload associated with application of the new IADPSG 2010 criteria based on data collected from multiple Sydney hospitals with a multicultural demography. It was found that the new diagnostic criteria would pose up to 31% increase in workload, which may even be an underestimate considering the study population consisted of mostly pregnant women who have had a positive 50g GCT whereas the IADPSG recommendation advocates for universal screening with the 75g 2 hour OGTT.

The corresponding economic impact of this increased incidence of diagnosis have been explored by a few studies. A prospective Spanish study(76) demonstrated that despite 3.5 times increase in the prevalence of GDM in their study population from 10.6% via the American Diabetes Association 1997 criteria to 35.5% via the IADPSG 2010 criteria, there was a reduction in various pregnancy outcomes in their whole hospital population, particularly in caesarean section and neonatal intensive care unit admission, which contributed to the cost effectiveness of adopting the IADPSG 2010 criteria. However it is not possible to determine whether the lower incidence of these outcomes was related to changes in obstetric practice. Other economic modelling based on incidence obtained from a selection of US data have shown that the IADPSG 2010 criteria would increase cost spending hence
were not cost-saving, but would remain cost effective if certain conditions such as long term benefits or a presumed estimate of 74.9% of efficacy of treatment was reached (88, 89). However, analysis from the National Institute of Health and Care Excellence (NICE) in the UK(17) showed a substantial increase in health cost associated with IADPSG 2010 criteria which made it unfeasible for its application. Based on this pragmatic approach of taking into account the economic consideration as well as the incidence and perinatal outcomes, the 2015 NICE guideline differed from the IADPSG recommendations by advising GDM screening only in those with risk factors, and the use of a 75g OGTT with thresholds set at fasting of 5.6mmol/L and 2hr of 7.8mmol/L. Given the different healthcare models and funding structure of each country, it is very difficult to compare one study against another, however the general trend appears that an increase in health care cost would arise from the increased incidence associated with the new criteria. Options to overcome this health resource issue have been proposed including alternative systems of care or a grading system to further stratify those at risk, (87) as without a clear resolution of this critical issue, ongoing fragmentation of diagnosis of GDM exists, leading to persisting confusion within the health care providers and the patient.

The issues described are the major controversies plaguing the uniform acceptance of the IADPSG 2010 criteria six years after its publication. A need for high quality interventional trial and local health system economic viability studies are needed to assess the validity and sustainability of adopting the new criteria. Until then, we will need to rely on data comparing pregnancy outcomes of pregnancies where GDM was diagnosed with IADPSG criteria, against GDM diagnosed by other criteria.

### 2.1.4 Adverse Pregnancy Outcomes

Gestational diabetes increases the risk of multiple short term and long term adverse effects on both the mother and the neonate. Adverse maternal perinatal outcomes consistently associated with GDM have included pre-eclampsia, pregnancy induced hypertension, caesarean section as well as delivery complications associated with neonatal macrosomia (1, 90). The degree of hyperglycaemia also appears to positively correlate with the risk of these adverse outcomes. Activation of the sympathetic system in states of insulin resistance, the increase in triglyceride in hyperinsulinism causing endothelial dysfunction, and the direct effect of hyperglycaemia on vascular tone have been hypothesized as possible mechanisms to
explain the association between GDM and hypertensive disease in pregnancy (91). However, a clear pathophysiology to link these two conditions is still lacking.

One of the most prominent long term sequelae of GDM for the mother is the substantial increase in risk of developing type 2 diabetes. It is estimated that women with past GDM are up to 7 times more likely to develop type 2 diabetes with a cumulative incidence of up to 70%, using older criteria for GDM (92-94). Risk factors for the progression to T2DM in women with past GDM include diagnosis of GDM before 22 weeks gestation, increasing parity, weight gain, and non-white ethnicity (95, 96). Even in women with prior GDM and normal BMI without type 2 diabetes postpartum, there is evidence of abnormal glucose regulation with higher OGTT levels compared to women without past GDM (97). From a physiology point of view, both insulin sensitivity and islet cell function have been shown to decline postpartum in women with prior GDM (96, 98). One of the hypothesis to explain the aetiology is that the genetic alleles associated with developing type 2 diabetes are also present in women with GDM, whilst the more alleles the women expressed, the higher the risk of developing type 2 diabetes (99). Thus rather than two separate conditions, women who have GDM and subsequently developing T2DM could be manifesting different stages of a spectrum of a particular phenotype characterised by a propensity for insulin resistance. In addition there is now growing evidence of metabolic disequilibrium in parameters that would increase cardiovascular disease in postpartum women with past GDM, such as higher blood pressure, triglyceride, and greater vascular resistance (100). Therefore, rather than a transient condition, women with past GDM embodies a group at a heightened risk of future metabolic disorders requiring more vigilant monitoring and modifiable risk management with the health professional.

The hyperglycaemic state of GDM also poses significant risk for the neonate in the antenatal and perinatal period. Increased rate of large for gestation (LGA), birth trauma, shoulder dystocia, prematurity, neonatal hypoglycaemia, hyperbilirubinaemia, erythrocytosis and stillbirth have been consistently observed in neonates of pregnancies complicated by untreated GDM, with many of these risks still persisting despite maternal treatment for GDM in pregnancy (1, 101, 102). In the landmark HAPO study (1) examining the relationship between maternal hyperglycaemia and adverse pregnancy outcome, it was found that the risk of adverse neonatal outcomes such as LGA is correlated to the level of maternal hyperglycaemia in a continuous positive linear fashion. The aetiology of LGA in pregnancy complicated by hyperglycaemia is hypothesized by Pederson to be due to the growth
stimulating effect of foetal hyperinsulinism in response to maternal hyperglycaemia, resulting in excess glucose passively diffusing across the placenta (103). As a result of LGA and macrosomia, vaginal delivery becomes difficult leading to increased risk of shoulder dystocia and associated Erb’s palsy, need for instrumentation in delivery, perineal tears, need for caesarean section and postpartum haemorrhage from uterine atony.

The long term effect of GDM on the offspring has been of growing interest with the increased understanding of the effect of intrauterine environment on the epigenetics of the foetus. Pettitt et al (104) had demonstrated in Pima Indians, a population with high incidences of diabetes and obesity, the offspring of women who had diabetes in pregnancy were up to 3 times more likely to develop diabetes compared to offspring of women without diabetes in pregnancy. Increased insulin resistance has also been demonstrated in offspring of mothers affected by GDM, in which over 19% of the children in one study cohort had developed impaired glucose tolerance by age 10. This rate was higher than children of non-diabetic mothers but similar to the offspring of women with pre-gestational diabetes (105). In addition, it was found that this outcome was independently associated with obesity and higher amniotic fluid insulin level during pregnancy (106). Obesity was also found to be increased in the offspring of pregnancy affected by GDM (107). However, one study found that GDM may not be an independent risk factor, but rather an effect modifier for the risk factor of maternal obesity to impart greater risk on the offspring to develop obesity (108). More recent evidence has emerged regarding an increased risk of metabolic syndrome in offspring of women with GDM (109, 110). It is unknown whether treatment of GDM in pregnancy would alter these long term adverse outcomes in the offspring, hence future research in this area is imperative to prevent a vicious cycle of intergenerational passage of metabolic dysregulation that would no doubt pose a significant strain on public health in the future.

2.1.5 Effect of Maternal BMI

2.1.5a Maternal BMI as a risk factor for developing GDM

The interplay between maternal weight and GDM influences the onset of GDM, adverse perinatal outcomes, as well as long term maternal and foetal outcome. Pre-pregnancy BMI is a significant risk factor for the development of GDM. A meta-analysis of 20 studies showed that the odds ratio for developing GDM were 2.14, 3.56 and 8.56 in women who were
overweight, obese and severely obese respectively (111). This positive relationship between increasing BMI and GDM development has also been consistently demonstrated in another meta-analysis study (112). From a pathophysiology point of view, using the euglycaemic-hyperinsulinaemic clamp study, Catalano et al demonstrated that obese women in pregnancy had decreased first and second phase insulin secretion in response to intravenous glucose infusion compared to lean women, speculating that this may represent relative beta-cell dysfunction imparted by the chronic insulin resistance associated with obesity (27). This predisposition to decreased beta-cell function is then further exacerbated by the hormonal influence of pregnancy in raising the insulin resistance, leading to a higher discrepancy between insulin sensitivity and insulin secretion, manifesting as GDM.

In addition to pre-gestational BMI, gestational weight gain has also been implicated as a risk factor for developing GDM. The Institute of Medicine (IOM) published a recommendation for gestational weight gain based on pre-gestational BMI categories in 2009 (113), however, the risk of developing GDM was not a consideration in the recommendation due to a lack of study on this subject at the time. Since then, multiple studies have demonstrated that the rate of weight gain from conception to around 24 weeks gestation has a positive relationship with the development of GDM, with the risk more pronounced in women with pre-gestation overweight and obesity. (114-116) This link between high BMI with development of GDM has significant public health implications whereby adequate resources need to be available to cope with the likely influx of women diagnosed with GDM given the climate of the obesity epidemic. In addition, there is currently a lack of effective management to reduce the risk of developing GDM (117), hence further research is necessary to develop interventional strategies.

2.1.5b Maternal BMI as an independent risk factor for adverse pregnancy outcome

The effect of high pre-gestational BMI imposes profound risks on perinatal outcomes in pregnancy. A Spanish study aiming to examine the independent effects of maternal glucose and pre-gestational BMI on pregnancy outcome had found that BMI above the overweight range exerts more risk to the development of LGA, macrosomia, caesarean section and pregnancy-induced hypertension than mild hyperglycaemia in women with GDM. (118) This result was again demonstrated on a sub-analysis of the women involved in the HAPO study which found that pre-pregnancy maternal BMI was associated with higher odds ratio, thus
greater influence on the occurrence of LGA and caesarean section than mild hyperglycaemia within the diagnostic criteria for GDM. In addition, this study showed that independent of maternal glucose levels, the relationship between increasing pre-gestational BMI and these adverse pregnancy outcomes was positively continuous and linear. (119)

Gestational weight gain has also been demonstrated to be associated with adverse pregnancy outcome in women with GDM. Compared to gestational weight gain kept within the IOM recommendation, women with GDM who had gestational weight gain above the recommendation were found to have increased risk of LGA, preterm delivery and primary caesarean section. (120-122) Moreover, there is evidence that moderate exercise in pregnancy is effective in limiting pregnancy weight gain as well as leading to an associated improvement in pregnancy outcome, lowering the risk of LGA, caesarean section, and maternal hypertension (123-125). These findings suggest that on top of the current dietary advice and glycaemic control as part of the multidiscipline management for GDM, there may be a role for the incorporation of an exercise regime to assist with targeting the optimal pregnancy weight gain to decrease adverse pregnancy outcome.

Moreover, there is the possibility that maternal obesity may act as a disease modifier in women with GDM. A recent study comparing the pregnancy outcomes of women with GDM who were successful in maintaining euglycaemia with diet and exercise versus women without GDM, found that despite treatment, the GDM group had higher risk of polyhydramnios and neonatal ICU admission and that this risk increased as the BMI category increased (126). The enhancement of adverse pregnancy risk in women with GDM and obesity was similarly demonstrated in study examining women with untreated GDM. Given this interaction effect, it raises the point that management of GDM to lower adverse pregnancy outcome cannot be relied upon purely via the control of the maternal BGL, and that weight management needs to be incorporated as part of the treatment in order to optimize pregnancy outcomes. The implication of the women’s pre-gestation weight as a risk factor in these studies is that obesity is an important pre-conception determinant of adverse pregnancy outcome and that it is imperative for the health professional to advise and counsel women regarding weight management during the planning stage of the pregnancy.
2.1.5c BMI and effect on post GDM development of Type 2 Diabetes

The interaction between maternal BMI and GDM does not cease with pregnancy, as weight gain during and post pregnancy in women with GDM compounds onto the existing risk of these women developing T2DM. This effect appears to be detectable soon after pregnancy. It was found that in women with GDM, increasing weight gain between the pre-pregnancy weight and the maternal weight at 1 – 6 months postpartum was an independent predictor of impaired glucose tolerance within 6 months postpartum, with every 10 pounds of weight gain being associated with an increased risk of impaired glucose tolerance by a factor of 1.67 (95). Rather than this being a transient effect, this risk persists in the long term. One study in Hispanic women with GDM found that over 12 years postpartum, for every 5kg of weight gain post pregnancy, the hazard ratio for developing T2DM was 1.67. This risk was similar to post pregnancy gain in body fat, suggesting that the effect exerted by weight gain is likely to be mediated by adipocytes. The author postulated that increasing insulin resistance associated with post pregnancy weight gain compounds the chronic post pregnancy beta-islet cell compensation failure in women with GDM, thus acting as a catalyst for the development of T2DM (96). From the evidence described, pre-gestational BMI, gestational weight gain, and post gestation weight gain all exert significant metabolic effects on women with gestational diabetes and may present as possible targets of intervention to improve the short term and long term maternal and foetal health outcomes.

2.1.6 Management of Gestational Diabetes

Multiple studies and systematic reviews have shown that treatment of maternal hyperglycaemia in pregnancy leads to improved perinatal outcome (73, 127). Observational studies have shown reduction in perinatal mortality since the commencement of treatment for GDM compared to historical data when GDM was untreated (128), though improvements in general perinatal care could have confounded such results. More recent prospective and retrospective observational studies using the IADPSG 2010 diagnostic criteria comparing the perinatal outcomes of women with treated GDM with those without GDM have found similar rates of LGA and primary caesarean section between the two groups (77, 78) when traditionally GDM was associated with higher risk of these adverse outcomes, hence suggesting possible benefit of treatment. However, randomised controlled trials have not been conducted using these criteria.
A combination of lifestyle changes in diet and exercise with the adjunct of insulin therapy are used as part of the regime for GDM management. Dietary factors not only impact on the immediate post prandial response based on the carbohydrate content, but caloric intake also affects the overall pregnancy weight gain and adiposity induced insulin resistance. The current consensus in dietary recommendation for GDM suggests a caloric intake of 2200 – 2400kcal per day for non-obese GDM women, mild caloric restriction of 33% reduction for obese GDM women, with carbohydrate intake limited at 35 – 45% of total calories preferring low glycaemic index carbohydrate foodstuff distributed across 3 main meals and 2 – 4 snacks (129-131). Exercise is known to increase muscular glucose uptake thus decreasing hyperglycaemia. Therefore a number of organizations recommend tailored moderate exercise regimes of 30 minutes per day on most days of the week (132, 133). The benefits of these lifestyle changes in improving perinatal outcomes in women with hyperglycaemia have been demonstrated in several studies (124, 134, 135). Though the sample size in many of these studies are small, a recent large retrospective study of 3066 women have yielded consistent findings which found that in women with GDM who only required diet and exercise for management, the perinatal adverse outcomes traditionally associated with GDM were comparable to women without GDM. In particular there were no difference in outcomes of pre-eclampsia, pregnancy induced hypertension, shoulder dystocia, caesarean section, and even a decreased LGA in the GDM cohort compared to women without GDM without an increase in SGA (126). Insulin therapy has been shown to effectively lower hyperglycaemia and improve adverse pregnancy outcome of LGA compared to those whose hyperglycaemia was suboptimally controlled with dietary management alone. (136) Its inability to cross the placenta to affect the foetus makes it the safer option compared to oral hypoglycaemic agents to be used as an adjunct in management of GDM.

On the other hand, the evidence for specific treatment targets for GDM is not robust due to the paucity of high level interventional trials and a lack of consistency across the selection criteria of the studies. As a result, the treatment target has differed across institutions and internationally, and remains a controversial issue. There have been few large interventional studies to assist with determining the glycaemic target for the antenatal period in the management of gestational diabetes. The Australian Carbohydrate Intolerance Study in Pregnant Women (73) was a major randomized control study of 1000 women with GDM comparing intervention with targeted glycaemic control versus routine care. Women were
defined as having GDM via a positive 50g oral GCT whereby a 1 hour BGL ≥ 7.8 mmol/L and a subsequent 75g OGTT with fasting BGL < 7.8 mmol/L and a 2 hour BGL 7.8 – 11.0 mmol/L were required. The target BGL in the intervention group was fasting and pre-prandial BGL ≤ 5.5 mmol/L, and 2 hours post prandial BGL ≤ 7.0 mmol/L. The intervention group was found to have significantly reduced primary perinatal composite outcome consisting of neonatal death, shoulder dystocia, bone fracture and nerve palsy. There was also less LGA, macrosomia > 4kg and antenatal pre-eclampsia. However, when examined as individual complications, there was no difference between the groups in the occurrence of shoulder dystocia or caesarean section. In addition, the intervention group had an increased rate of induction of labour and neonatal nursery admission.

A similar randomised controlled trial by the Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal–Foetal Medicine Units Network (74) consisting of 958 women with mild GDM was conducted aiming to compare the pregnancy outcomes between those given standard perinatal care versus more intensive glycaemic control via diet and or insulin. The glycaemic criteria for diagnosis of mild GDM in this study were women who had a 50g GCT with a 1 hour result of 7.5 – 11.1 mmol/L and a 3 hour 100g OGTT with fasting < 5.3 mmol/L, and two or three timed glucose results exceeding the levels of 1hr 10.0 mmol/L, 2 hrs 8.6 mmol/L, 3 hrs 7.8 mmol/L. In the intervention group, glycaemic control targets were set at fasting BGL < 5.3 mmol/L and 2 hour post prandial BGL < 6.7 mmol/L. There was no significant difference between the control and the intervention group in the primary composite outcome consisting of perinatal mortality, neonatal hypoglycaemia, hyperbilirubinaemia, neonatal hyperinsulinaemia and birth trauma. However, there was compelling evidence of decrease in LGA, shoulder dystocia, caesarean section, gestational hypertension and pre-eclampsia in the intervention group.

Unfortunately, given the different selection criteria used to define GDM in the various studies, it is difficult for comparison to occur between the studies. In addition, the 2 large interventional studies were investigating women who all had hyperglycaemia following pre-screening with a glucose load (by virtue of the 50g GCT) hence they are not representative of all women with GDM by the IADPSG criteria. The current recommendation from the ADIPS suggests target BGL of fasting ≤ 5.0 mmol/L, 1 hour post prandial BGL ≤ 7.4 mmol/L, and 2 hour post prandial BGL ≤ 6.7 mmol/L (52). These values were derived from a combination of epidemiological data in normal pregnant women extrapolating 2 standard deviations above.
the mean, as well as data from the HAPO study and the existing interventional trials on treatment of GDM.

Even though the hyperglycaemia in GDM resolves after delivery, women with GDM are at increased risk of future health risks associated with insulin resistance. Women with GDM are at increased risk of GDM in future pregnancies with systemic reviews showing a recurrence rate of between 30 – 84%, with the higher recurrence rates occurring in ethnic minority groups compared to non-Hispanic white ethnicity (39). Moreover, women with GDM have up to 7 fold risk of developing type 2 diabetes. Depending on duration of follow up and study population ethnicity, the cumulative incidence of subsequent type 2 diabetes could be up to 70% (92-94, 137). As a result of these long term risks, the current ADIPS guideline (52) recommends a 75g OGTT to be performed at 6 – 12 weeks postpartum for early detection of type 2 diabetes. In addition, an annual OGTT is recommended in women who have had past GDM and contemplating future pregnancies to assess for early signs of insulin resistance that may affect the pregnancy so treatment may be instigated early. In the long term, women with GDM should be screened at regular intervals of every 1 – 2 years using methods such as HbA1c, fasting BGL or a formal OGTT to detect development of type 2 diabetes.

2.1.7 Research Directions

From this review of evidence, GDM is associated with multiple foetal and maternal adverse pregnancy outcomes on the short term as well as long term. In addition, other metabolic factors, such as maternal obesity, which has a high prevalence in women with GDM, compound the risk for adverse pregnancy outcome. There is some evidence of potential efficacy in treatment of GDM to improve pregnancy outcome. However there is a lack of universally accepted diagnostic criteria to identify women at risk, given the relatively new introduction of the IADPSG 2010 criteria, which undermines the first step in the process to achieve improvement in pregnancy outcome in this population. Part of the controversy arises from the lack of evidence in evaluating the ability of the new diagnostic criteria to identify the women at risk of adverse outcome compared to the existing ADIPS 1998 criteria. Thus, research efforts to address this issue is integral in the scheme to improve maternal and foetal welfare, as well as reaching efficiency in healthcare policy making and planning.
2.2 Peripartum Glucose Control and Neonatal Hypoglycaemia

2.2.1 Pathophysiology

Neonatal hypoglycaemia can be divided into two main types, transient and persistent based on duration of the recurrence of the hypoglycaemia. The causes of transient hypoglycaemia can be physiological or acquired. In utero, the passive diffusion of maternal glucose across the placenta into the foetal circulation provides the foetal supply of glucose for growth, thus during this time, the foetal blood glucose correlates with maternal blood glucose. In response to the glucose, the foetal pancreatic islet cells are capable of producing insulin for metabolism of the glucose as well as exerting an anabolic effect for foetal growth and development. Upon delivery, the maternal glucose supply is removed and the neonate’s fuel supply for metabolism becomes dependent on the processes of gluconeogenesis, glycogenolysis as well as mobilization of fatty acids from adipose stores (138). A physiological decrease in blood glucose level (BGL) occurs after birth, which in term neonates of appropriate gestational size usually reaches 3.0 – 3.3mmol/L but has been observed to be as low as 1.6 mmol/L, followed by a steady rise and stabilization after the first 24-48 hours of birth. (139-141) This decline in glucose level is most prominent in the first 1-3 hours of life. (142) This transient physiological decrease in blood glucose level in the neonate upon transition from intra-uterine life to extra-uterine life is referred to as transitional hypoglycaemia (Figure 2). This occurrence is hypothesized to be due to altered thresholds for insulin suppression and glucagon activation in the neonate (141). The threshold for suppression of insulin is lowered in the neonate in the days following birth, leading to relative hyperinsulinaemia. This conclusion was drawn from the observation that the initial hypoglycaemia was a hypoketotic event with the presence of increasing ketones occurring only after 24 – 48 hours. This was thought to be carried over from the adaptive role of the foetus in utero whereby ongoing neonatal insulin secretion during periods of maternal overnight fasting would allow maintenance of foetal growth while the foetal brain could be fuelled by maternal ketones during the period. Also, there appears to be a lowered threshold for glucagon activation as a glucagon response was still able to be elicited post exogenous glucagon administration, indicating that there is presence of liver glycogen stores which had not been sufficiently activated despite the lowered blood glucose level. This process is further
modulated by the degree of ability of the neonatal sympathetic homeostatic system and adequacy of glycogen storage to mount a counter response to the hypoglycaemia (138).

Figure 2: Physiology of Transient Neonatal Hypoglycaemia

Acquired neonatal hypoglycaemia is usually transient and occurs when there are external influences that result in increased risk of occurrence of neonatal hypoglycaemia. Prematurity may be associated with immaturity of the gluconeogenesis and ketogenesis systems imparting the higher risk of hypoglycaemia (138). This is further compounded by the lack of adipose tissue which is mainly deposited in the last few weeks of pregnancy, creating an over-reliance on gluconeogenesis for the fuel of metabolism (143). Peripartum stress especially birth asphyxia, and delayed feeding depletes hepatic glycogen stores and thus impairs adequate glycogenolysis to maintain euglycaemia (144). In addition, hyperinsulinaemia has been found in neonates that are small for gestation contributing to their risk of hypoglycaemia(145).

One major cause of acquired neonatal hypoglycaemia is maternal pre-gestational diabetes. The incidence of neonatal hypoglycaemia in women with diabetes has been observed to be from 48 – 71% whereas the incidence in normal term infants has been documented between 10 – 38%, though these incidence rates may be confounded by the use of different thresholds to define hypoglycaemia in these studies (139, 146-148). The pathophysiology of this hypoglycaemia was first propositioned by Pederson whereby maternal hyperglycaemia leads to neonatal hyperinsulinaemia contributing to foetal macrosomia and hypoglycaemia upon delivery when the continuous maternal glucose supply is removed (103, 149). When using
cord c-peptide as a surrogate marker of neonatal insulin release, it was found to have a positive continuous linear relationship with the maternal OGTT, supporting the Pederson hypothesis (1).

Persistent neonatal hypoglycaemia manifests as recurrent or persisting severe symptomatic hypoglycaemia beyond 7 – 14 days of delivery and usually has a congenital genetic aetiology that is dependent on medical treatment (150). Congenital hyperinsulinism is the most common aetiology with multiple genetic defects implicated (Table 5) (151).

Table 5: Genetic Mutations Associated with Congenital Hyperinsulinaemia

<table>
<thead>
<tr>
<th>Pathophysiology of genetic mutation</th>
<th>Impairment of insulin production/release</th>
<th>Mitochondrial abnormality</th>
<th>Pyruvate transporter abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic Mutation</td>
<td>ABCC8</td>
<td>HADH</td>
<td>SLC16A1</td>
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<tr>
<td></td>
<td>KCNJ11</td>
<td>UCP2</td>
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<td>HNF1A</td>
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The high prevalence of neonatal hypoglycaemia in Beckwith-Wiedemann syndrome has also been attributed to the hyperinsulinaemic mechanism (152). Apart from hyperinsulinism, other congenital defects along the pathway of glucose formation, consumption and regulation can also result in persistent neonatal hypoglycaemia (153). An absence of functional enzymes for gluconeogenesis such as fructose-1,6-bisphosphatase or phosphoenolpyruvate carboxykinase can lead to severe hypoglycaemia, ketosis and lactic acidosis especially in febrile illness. The inability for glycogen formation such as in glycogen synthase deficiency, or the inability for hepatic glycogenolysis such as in the glucose-6-phosphatase deficiency associated glycogen storage disease type 1, are characterized by fasting and post prandial hypoglycaemia respectively. Abnormalities in fatty acid oxidation results in a lack of ketone production as an alternative fuel for tissue metabolism leading to a reliance and subsequent
overconsumption of glucose causing a state of hypoketotic hypoglycaemia. Moreover, systemic conditions affecting the hormonal activation of the adrenergic system such as hypopituitarism, adrenal insufficiency and hypothyroidism can also cause neonatal hypoglycaemia. This diversity of congenital conditions causing neonatal hypoglycaemia not only gives insight into the complex pathways regulating the homeostasis of blood glucose but also the importance of understanding this genotype and phenotype correlation in order to assist with treatment and genetic counselling. Despite our current knowledge, studies have reported more than 20-50% of the children with congenital hypoglycaemia in the study sample without a known genetic mutation (151, 154), demonstrating an area of knowledge gap to be filled by future research.

2.2.2 Adverse effects of neonatal hypoglycaemia

Much of the controversy in determining a numerical threshold for diagnosis and the need for treatment of neonatal hypoglycaemia is related to the limited and inconsistent knowledge regarding the short term and the long term adverse effects of hypoglycaemia on the neonate. Cerebral vulnerability in states of hypoglycaemia is the main concern given the dependence on glucose metabolism as a major substrate for production of ATP in neuronal cellular function. Biopsy of neonates who died from untreated hypoglycaemia revealed effects predominantly on the occipital cerebral cortex (155). This predominant posterior cerebral involvement in hypoglycaemia has also been substantiated by MRI imaging, which has also revealed a more diverse range of territories involved in hypoglycaemia damage including a large proportion of white matter infarct and haemorrhage, basal ganglia lesions and even middle cerebral artery territory infarctions. (156) This use of investigative technology has played a significant role in transforming our understanding on the adverse effects of hypoglycaemia on the neonate.

The term symptomatic neonatal hypoglycaemia defines the manifestation of immediate adverse symptoms ranging from recurrent apnoea, vomiting, poor feeding, irritability, jitteriness, hypothermia to severe convulsions and coma in the setting of low neonatal blood glucose level. (150) Neonates with symptomatic hypoglycaemia, especially with neurological symptoms, sustain more severe permanent neurological damage (157). MRI studies on neonates with hypoglycaemia <2.1mmol/L with neurological manifestations have exhibited white matter abnormalities in up to 94% of these neonates of which 43% were classified as
severe. (156) Hence alleviation of symptoms and preventing severe neurological damage are major indications for treating symptomatic hypoglycaemia. However using symptomatic hypoglycaemia alone as the basis for diagnosis and treatment of hypoglycaemia may be problematic. Firstly, most symptoms of hypoglycaemia are non-specific and many are subjective. In one study of 661 preterm neonates, the prevalence of symptoms that are usually associated with hypoglycaemia was the same in the hypoglycaemic neonates as well as the non-hypoglycaemia neonates, highlighting the poor specificity of the symptoms (158). Moreover, these symptoms occurred inconsistently across a wide range of glucose levels and may only occur a significant amount of time after a severe low glucose level has developed(159). Thus a symptom focused approach to treatment could potentially result in a delay in treatment and miss a significant proportion of neonates with asymptomatic hypoglycaemia.

The clinical significance of asymptomatic hypoglycaemia has been an issue of much debate. Higher risk of the development of an abnormal evoked potential has been observed in neonates with hypoglycaemia <2.6mmol/L, with half of the neonates who demonstrated the abnormality being clinically asymptomatic during the event of hypoglycaemia (160). Diffusion restriction in the occipital lobe on MRI within 6 days of the hypoglycaemic event has been shown to occur in neonates with hypoglycaemia <2.1mmol/L, which clinically corresponded to an increased risk of abnormal visual evoked potential at 1 weeks post hypoglycaemic event (161). These investigation abnormalities were used as surrogate markers for neuronal damage, but whether they correlate with clinical permanent impairment is unknown.

Part of the difficulty in setting a threshold for diagnosis and treatment of neonatal hypoglycaemia is the controversy regarding the resilience of the neonatal brain to cope with the hypoglycaemia. Stanley et al drew comparison between the lowered insulin secretion threshold in transitional neonatal hypoglycaemia with infants with glucokinase mutation that also decreases the insulin secretion set point. It was suggested that as observed in neonates with glucokinase mutation that despite the threshold for insulin inhibition at close to the neuroglycopenic range, these neonates will still be able to mount a compensatory response in time to prevent glycopenic brain damage (141). In addition, term neonates have been shown to have the ability to utilize ketones, lactates and fatty acids as alternative fuels thus conferring protection to the brain in glycopenic situations (138, 162). Hence some authors have argued against the use of a numerical threshold to define clinical significance in
neonatal hypoglycaemia but to take into account the ability of the neonate to mount a counter-regulatory response for homeostasis and the presence of alternative fuels when deciding the need for medical intervention (138). The emerging longitudinal studies examining the long term outcomes of neonates with hypoglycaemia have also contributed evidence towards this topic of the ability for cerebral recovery from hypoglycaemic assault. Long term neurological deficits such as speech delay, learning difficulties, psychomotor delay, visual deficits, motor deficits and pharmaco-resistant epilepsy have been associated with congenital hypoglycaemia. The aetiology of congenital hypoglycaemia, presence of acute comorbidity such as hypoxic-asphyxia or infection, and presence of status epilepticus have been found to be the main determinants of neurological sequelae severity in this population (163). When hypoglycaemia was defined as <2.8mmol/L, the level of hypoglycaemia did not appear to predict severity of long term adverse effect. Another follow up study of 26 neonates with congenital hyperinsulinaemic hypoglycaemia found presence of neurological deficit such as motor disability, seizures, brain damage and reduced IQ in 10 of the neonates, of which most occurred in patients who required surgical treatment for the congenital hypoglycaemia (164). Other studies in congenital hyperinsulinaemic neonates with hypoglycaemia have reported development delay ranging from 0 – 70%, with differences in delay in diagnosis and treatment causing prolonged and more severe hypoglycaemia being possible explanations for this wide range (165). Depending on the mechanism of congenital hypoglycaemia, these neonates may lack an adequate counter regulatory response to hypoglycaemia thus increasing their susceptibility to the neurological defects. Also ongoing assault from hypoglycaemia could have occurred beyond the neonatal age given the persistent nature of the pathology often requiring ongoing medical treatment. Thus these findings cannot be validly applied to non-congenital hypoglycaemic neonates.

The long term effect of non-congenital transient neonatal hypoglycaemia is a topic of much controversy due to inconsistency of evidence. In a study of preterm neonates, Lucas et al found that the frequency and the number of days of recurrence of hypoglycaemia may have an effect on neurodevelopment. Reduced developmental scores at 18 months in preterm infants were shown to be independently associated with the number of days on which blood glucose level was <2.6mmol/L. This study also showed that worse neurodevelopmental impairment occurred in neonates who had more frequent hypoglycaemia than those with more severe hypoglycaemia but at less frequency (158). This result was again replicated in a study of preterm neonates who were small for gestation (166). The analysis of a Dutch study
in moderately preterm neonates showed the lower the hypoglycaemia level, the more severe the parental reported developmental delay at pre-school, with the effect most prominent when BGL<1.7mmol/L (167). On the other hand, a similar study to the Lucas et al study conducted by Tan et al in preterm neonates was not able to reproduce the same result (168). In the latter study, recurrent neonatal hypoglycaemia<2.6mmol/L was not found to be associated with poorer neurodevelopmental outcome at 2 years and 15 years. In the preterm population, higher vulnerability to neurological damage may be conferred by physiological factors associated with neonatal immaturity, thus studies in this high risk cohort may not be translatable into the normal termed neonate population.

In a study of a cohort of term neonates that were large for gestation, no difference in neurodevelopmental outcome at 4 years was found between the hypoglycaemic group who had BGL<2.6mmol/L in the first 24 hours of birth and the group without hypoglycaemia (169). More recently, a large study comprising 614 neonates with risk factors for hypoglycaemia did not find evidence of neurodevelopmental impairment at 2 years in the hypoglycaemic cohort including those with recurrent hypoglycaemia and severe hypoglycaemia. (170) Yet functionally, a large study of 1395 term neonates found that hypoglycaemia <2.5mmol/L was associated with a decrease in literary and mathematics achievement test proficiency at 10 years of age. (171) Comparison between studies of different follow up periods is difficult as potential catch up in neurodevelopment can occur that may annul a previous finding performed at a younger age. In addition, there is heterogeneity between the studies in the study population, operational threshold for treatment of the hypoglycaemia, and the tests that were used to assess aspects of psychometric development between studies, preventing valid pooling of data on this topic in previous attempts at systemic analysis on this topic (172). As a result of the inconsistency of results demonstrated by the various studies, it is difficult to reach a consensus on the long term clinical significance of transient hypoglycaemia and the threshold at which neurological sequelae arise.

### 2.2.3 Management of neonatal hypoglycaemia

Given the complex difficulty surrounding attempts to define the threshold for treatment of neonatal hypoglycaemia with a numerical value, there is currently no consensus on a particular operational value to initiate treatment that will effectively prevent short term
symptoms and long term neurological impairment, whilst specific enough to avert unnecessary interventions that are wasteful, prolong admission and impact on maternal bonding with the neonate. In a conservative approach, most guidelines have used <2.6mmol/L (47mg/dL) as a level at which the clinician should be aware of the potential need for intervention, as most studies on adverse outcomes have been based around this value.

Screening procedures have been published to detect the onset of hypoglycaemia in neonates. The American Academy of Paediatrics 2011 recommendation(173) suggests routine screening to be undertaken only in at-risk neonates which comprises those that are born premature and small for gestation in the first 24hours of birth, neonates of diabetic pregnancy and large for gestation in the first 12 hours of birth. Other neonates at risk of hypoglycaemia should be determined for monitoring at the judgement of the clinician. Screening should commence within the 1st hour of delivery, and in late preterm and small for gestation neonates, be continued at intervals of every 2 – 3 hours before each feed. Ongoing monitoring beyond 24hours should be performed in those who persisted to have BGL<2.5mmol/L. If a low BGL is detected via monitoring, it should be confirmed with a formal peripheral plasma glucose level, however this process should not delay any intervention. In this publication, a higher priority has been given to treat neonates with symptomatic hypoglycaemia given the need to ameliorate the symptom as well as preventing the risk of neuronal injury, especially in cases of neurological symptoms such as convulsions. Based on this, all symptomatic neonates with an arbitrarily set value of BGL<2.2mmol/L are recommended to be treated with intravenous (IV) glucose. Other guidelines have also echoed the same sentiment regarding screening only in at-risk neonates as well as prioritizing neonates with symptomatic hypoglycaemia, however the timing of commencement of screening have slight variations from 2 – 4 hours of age (174, 175).

2.2.3a Guidelines for Management of Neonatal Hypoglycaemia

Interventions for raising the BGL in the neonate vary in intensity based on the urgency to correct the hypoglycaemia. In the asymptomatic neonate, initial oral intake via breastfeeding, supplementary nutrition feed or glucose using 5% solution at a volume of 10mL/kg have been proposed (150, 175, 176). More recently, 40% dextrose gel administered to the neonate’s buccal mucosa has shown potential to be an effective alternative that has less treatment failure rates than feeding alone in correction of hypoglycaemia (177). Based on the American
Academy of Paediatrics 2011 guideline (173), asymptomatic hypoglycaemic neonates could be managed with oral feeding upon their first presentation and rechecking of BGL 30 minutes after the 1st feed aiming for a target of 2.2 – 2.8mmol/L which should be high enough to prevent neuronal damage but lower enough to deter further insulin secretion. Upon recurrence of hypoglycaemia, the need for IV glucose could be considered at higher BGL ranges of 1.9 – 2.2mmol/L, and recommended at lower BGL ranges of <1.9mmol/L. IV glucose can be given as a bolus of glucose dose of 200mg/kg (dextrose 10% at 2mL/kg), or an infusion of glucose dose 5-8mg/kg/minute (dextrose 10% at 80 – 100mL/kg/day). In neonates requiring prolonged or high dose dextrose infusion, sodium and potassium containing solutions need to be introduced to maintain electrolyte balance and prevent iatrogenic hyponatraemia (150). A similar principle of a gradual upgrade in degree of intervention based on clinical symptoms, duration, and severity of hypoglycaemia was proposed in the Canadian Paediatric Society and the Academy for Breastfeeding Medicine guidelines for management of neonatal hypoglycaemia (175). In symptomatic neonates, upon improvement of the glucose level, it is important to reassess the neonate for resolution of symptoms to fulfill a diagnosis of symptomatic hypoglycaemia via Whipple’s triad whereby the symptom occurs in the setting of a low blood glucose level and resolves upon improvement of the blood glucose level. Given the non-specific nature of symptoms associated with hypoglycaemia and the comorbidities that are associated with increased risk of hypoglycaemia, should the symptoms persist beyond correction of the hypoglycaemia, hypoglycaemia may not be the contributor of the symptoms and alternative causes should be investigated. Currently there is no uniform Australian guideline for the management of neonatal hypoglycaemia.

2.2.3b Treatment of congenital hypoglycaemia

Should hypoglycaemia be recurrent or persist beyond 5 – 7 days of birth, or the need for IV glucose exceed 10-12 mg/kg/min, causes of persistent hypoglycaemia such as congenital hyperinsulinaemic hypoglycaemia, inborn errors of metabolism, or systemic endocrine pathology need to be considered (150). Diagnostic work up includes a family history, physical examination for signs of systemic endocrine disorders, and basic investigations include bicarbonate, lactate, free fatty acid, and beta-hydroxybutyrate levels should be obtained to assist with deciphering the potential aetiology of the persistent hypoglycaemia.
and planning further diagnostic tests (178). In cases of persistent hypoglycaemia, the use of high dose IV glucose may not be sufficient to maintain euglycaemia and additional agents may be required such as glucagon given IV in a bolus of 0.1 – 0.3mg/kg or infusion 10 - 20µg/kg/h, hydrocortisone, diazoxide, or octreotide (175). The Pediatric Endocrine Society recommends treatment in persistent hypoglycaemia to target a plasma glucose level of >50mg/dL (2.8mmol/L) in neonates <48hours age and >60mg/dL (3.3mmol/L) in neonates >48hours of age in order to avoid recurrent activation of the hypoglycaemic neuroendocrine response that may lead to development of hypoglycaemic-associated autonomic failure (178). Long term management of persistent hypoglycaemic disorders depend on the aetiology, with treatments ranging from avoidance of fasting, replacement of deficient hormone, to surgical pancreatectomy.

2.2.3c Side Effects of Treatment

To further deepen the debate into the screening and treatment of neonatal hypoglycaemia, there has been emerging evidence of the potential harm of treatment. Resource wastefulness had been a major concern of overtreatment of hypoglycaemia in the past, as the treated neonates would usually be monitored in an intensive care environment. More recently it has been recognized that over-surveillance by removing the neonate from the mother and inappropriate treatment with early formula supplementation may lead to potential harm in the infant maternal bonding relationship and disrupt the breastfeeding experience with a delay in lactogenesis, impaired breastmilk production and a lowered maternal confidence in the nutritional value of breastfeeding (179). As healthy term neonates exclusively breastfed are known to have a lower BGL than those on supplemental feed yet protected from neurological harm due to higher ketone bodies, this represents a group that may be at high risk of unnecessary treatment and interference with the breastfeeding experience (180). In addition, a recent study has revealed a novel finding of higher glucose levels, albeit still within the normoglycaemic range for neonates, especially when associated with fluctuations due to treatment of an initial hypoglycaemic event, may be linked with neurosensory impairment at 2 years. (170) The author hypothesized that possible mechanism of this phenomenon may be related to the production of reactive oxygen species causing neurological damage, and drew similarities with the poor mortality associated with patients with high glucose variability in the ICU setting. However, given the exclusivity of this finding to the one study, the presence...
of this adverse effect needs to be confirmed as it has a clinical impact on treatment methods for hypoglycaemia.

2.2.4 Maternal glycaemic control and neonatal hypoglycaemia

Given the increased risk of neonatal hypoglycaemia associated with maternal diabetes, several studies have investigated different aspects of maternal glycaemic control as possible predictors of neonatal hypoglycaemia in order to determine potential modifiable risk factors. As controversy developed regarding the relative importance of intrapartum maternal glycaemic control versus antepartum glycaemic control in association to neonatal hypoglycaemia, the use of an insulin-dextrose infusion for women with diabetes in labour has emerged into practice in an effort to modulate the risk of neonatal hypoglycaemia.

It has been consistently found in the literature that the first neonatal blood glucose at birth is highly positively associated with the last maternal glucose at delivery. Pederson, who pioneered the notion of hyperinsulinaemic neonatal hypoglycaemia in pregnancies affected by maternal diabetes, had also brought into attention the relationship between maternal glucose levels in the intrapartum period with the neonatal glucose level at delivery. His observational study found that the last maternal blood glucose before delivery was highly positively correlated with the first neonatal glucose at delivery (149). This is likely to be explained by the continuity of passive diffusion of maternal glucose across the placenta into the foetal circulation throughout labour until the umbilical cord is cut at delivery, as a strong association between the maternal BGL during labour and the umbilical vein BGL had been demonstrated both in diabetic and non-diabetic pregnancies (181, 182). This is further reinforced by prospective studies whereby mothers without diabetes were given a glucose infusion at delivery which resulted in both higher maternal blood glucose, higher foetal scalp capillary glucose at labour (183), and higher umbilical vein glucose at birth compared to control (184). This highlighted not only the presence of a physiological process, but also demonstrated that the intrapartum neonatal blood glucose level may be modifiable by aspects of maternal intrapartum glucose.

There is competing evidence regarding the relative contributions of antepartum and intrapartum maternal glycaemic control to neonatal hypoglycaemia. Understanding these relative contributions is important in identifying those at risk of neonatal hypoglycaemia to
facilitate prevention, monitoring and expedite treatment. Improvement in antepartum glycaemic control had traditionally been known to reduce adverse pregnancy outcomes in women with diabetes, and may also have a role in preventing neonatal hypoglycaemia. Higher HbA1c in the 2nd and 3rd trimester have been found to increase the risk of neonatal hypoglycaemia in women with insulin-dependent diabetes (185). To further support this, a randomised control trial on a group of GDM and pre-gestational diabetes mothers had demonstrated that a basal bolus regime of insulin administration improved antepartum glycaemic control compared to a twice daily insulin regime and significantly decreased the rate of neonatal hypoglycaemia in both GDM and pre-gestational diabetes women (186).

Several studies have now found an association between intrapartum maternal glycaemic control and the risk of neonatal hypoglycaemia. Andersen et al (181) had observed that in pregnancies affected by diabetes, there was a negative correlation between the maternal BGL and the neonatal BGL at 2 hours of birth. Curet et al (187) had shown that in 233 women with insulin-requiring diabetes, the average intrapartum glycaemic control had a stronger association than antepartum glycaemic control with neonatal hypoglycaemia, with the lowest risk if intrapartum maternal BGL was <5.6mmol/L. When specifically examining aspects of intrapartum glycaemic control, a study of 85 GDM women found that higher maximum maternal BGL during labour, within 4 hours of delivery and the mean BGL in the last 2 hours of delivery were independent risk factors for neonatal hypoglycaemia (188). On the other hand, Barrett et al(189) and Njenga et al(190) did not find a correlation between intrapartum maternal glycaemic control and risk of neonatal hypoglycaemia when maternal intrapartum BGL was targeted between 4 – 8mmol/L and 3 – 6mmol/L respectively.

Some have suggested a threshold effect for the association between intrapartum maternal hyperglycaemia with neonatal hypoglycaemia. A prospective observational study by Mendiola et al in non-diabetic women had shown a correlation between an increased risk of neonatal hypoglycaemia with maternal hyperglycaemia greater than 7mmol/L in the intrapartum period induced by glucose infusion (182). An observational study in women with type 1 diabetes by Carron-Brown et al had shown an increased risk of neonatal hypoglycaemia if maternal BGL was greater than 8mmol/L in labour, with that risk rising to 100% if the maternal BGL was greater than 10mmol/L. (191) This increased risk conferred by the threshold of intrapartum maternal glucose >8mmol/L was consistent with findings by Taylor et al (192) on a group of women with type 1 diabetes. A prospective observational study on 129 GDM women by Flores-le Roux et al in 2010 had not demonstrated association
with intrapartum glycaemic control and neonatal hypoglycaemia(193), yet when a similar study was conducted in 2012 on 190 GDM pregnancies, an increased risk of neonatal hypoglycaemia was found if intrapartum maternal BGL>7.2mmol/L(194). The concept of the threshold effect could perhaps explain the negative findings in Barret et al (189) and Njenga et al (190) where maternal intrapartum glycaemia was already well controlled.

Other studies examining both antepartum and intrapartum glycaemic control have yielded mixed results. Kline et al (195) found that in women with pre-gestational diabetes, intrapartum maternal BGL>6mmol/L predicted the occurrence of neonatal hypoglycaemia while the severity of the hypoglycaemia was determined by a 3rd trimester maternal HbA1c>6.5%. Both the Carron-Brown et al study (191) and the Taylor et al (192) study which had shown intrapartum glycaemic control as predictors of neonatal hypoglycaemia had also examined antepartum glycaemic factors such as maternal HbA1c at the three trimesters and did not find an association with these antepartum factors. On the other hand, a study by Agrawal et al (147) showed no correlation between either the average maternal fructosamine level in pregnancy or intrapartum maternal BGL with neonatal hypoglycaemia. Possible explanations for the inconsistency of results include small sample size of the studies, different thresholds used for the definition of neonatal hypoglycaemia, heterogeneous study populations consisting of women with pre-gestational and gestational diabetes, and different variables used for multivariable analysis. Given the difficulty in practicality and the ethics surrounding this study population, there is a paucity of randomized control trials on this topic, thus best available evidence would only come by quality observational studies.

2.2.4a Role of Insulin-Dextrose Infusion

Given the plausibility that maternal intrapartum glycaemic control may influence the risk of neonatal hypoglycaemia, an insulin-dextrose infusion has been utilized as a means to control intrapartum glycaemia. The insulin infusion allowed for control of glycaemia while the dextrose infusion prevented hypoglycaemia in labour given the high energy requirement during the process, as well as preventing dehydration and starvation ketosis in women fasting for caesarean (196), and ketoacidosis in women with type 1 diabetes. Both Coustan et al (197) and Caplan et al (198), had tested the use of an insulin-dextrose infusion in labour in the 1980s in women with diabetes and found it a flexible and practical means to control intrapartum maternal glycaemia and resulted in a decrease in neonatal hypoglycaemia.
similar result was redemonstrated in Lepercq et al (199) study in 2008 whereby euglycaemia was achieved in women with type 1 DM in labour using an insulin-dextrose infusion and resulted in a low rate of neonatal hypoglycaemia of 13%. Maternal hypoglycaemia is a potential side effect of tight glycaemic control during labour. Kline et al (195) observed that in women with diabetes on insulin-dextrose infusion during labour, there was an increase in symptomatic maternal hypoglycaemia, however the overall rate of maternal hypoglycaemia was not increased. Given this evidence, the use of insulin-dextrose infusion during labour has become a mainstay of practice for maternal glycaemic control at many institutions. Newer technology are now being explored, such as the continuous insulin pumps which have shown potential to provide better control than insulin-dextrose infusion and thereby subsequently lower the risk of neonatal hypoglycaemia (200). This is a growing area as its adjunct use with continuous glucose monitor may provide a method of maternal glycaemic control that is less labour intensive and reduces the risk of maternal hypoglycaemia.

2.2.5 Research Directions

Whilst many controversies surround the topic of neonatal hypoglycaemia, from its pathological diagnostic threshold, long term clinical sequelae, to treatment options, prevention is the first step to minimize its occurrence. Despite its increased frequency in neonates of women with pre-gestational diabetes, there is a paucity of knowledge regarding which aspect of maternal pre-gestational diabetes confers the greatest risk on to the neonate. It is important to explore the different parameters of maternal glycaemic control to determine the contributory role of intrapartum, antepartum, and variability of maternal glycaemic control towards the development of neonatal hypoglycaemia. This may help support the development of management protocols for the prevention and management of neonatal hypoglycaemia in diabetic pregnancy.
3. Study: Comparison of Adverse Pregnancy Outcomes Based on the New IADPSG 2010 Gestational Diabetes Criteria and Maternal Body Mass Index

3.1 Introduction

The diagnostic criteria for gestational diabetes (GDM) has evolved through the decades based on our increased understanding of the risks associated with this state of carbohydrate intolerance first recognized during pregnancy (58). The first diagnostic criteria was formulated in the 1964 based on the subsequent maternal risk of postpartum type 2 diabetes (8), rather than on the likelihood of obstetric outcomes. Subsequent criteria (10, 13) have been based on variations of the 1964 O’Sullivan and Mahan criteria, variations of the diagnostic criteria for diabetes mellitus in general (14), or in the case of the 1991 (12) Australasian Diabetes in Pregnancy (ADIPS) criteria, based on epidemiological statistical distributions of serum glucose in pregnancy.

Seeking to determine criteria for GDM based on pregnancy outcomes, the 2010 International Association for Pregnancy Study Groups (IADPSG) guideline (16) has used data from the HAPO study (1), which had examined the relationship between the glucose tolerance test and pregnancy outcomes. The diagnostic glycaemic levels were formulated based on an odds ratio of 1.75 to the adverse outcomes of neonatal LGA, primary caesarean section, neonatal hypoglycaemia and neonatal cord c-peptide > 90th centile. ADIPS and The Royal Australian and New Zealand College of Obstetricians and Gynaecologists have now adopted these criteria. Compared to the previous 1998 ADIPS criteria the changes include the elimination of the 50g oral GCT, universal screening at 24-28 weeks gestation with 75g OGTT, lowering of the fasting diagnostic BGL to ≥5.1 mmol/L, introduction of a 1hr post 75g OGTT BGL ≥10 mmol/L, and increasing the threshold for 2hr post 75g OGTT BGL to ≥8.5 mmol/L. The treatment targets have also been lowered to fasting BGL ≤ 5.0 mmol/L, 1hour post prandial BGL ≤ 7.4 mmol/L and 2hour BGL ≤ 6.7 mmol/L, with these values extrapolated from threshold of 2 standard deviations above the mean in pregnant women without risk factors in the HAPO study.
Controversies surrounding this new diagnostic criteria have resulted in the failure for it to be universally accepted in Australia, US and the UK. The observational nature of the HAPO study and the lack of randomised control trials into the benefits of treatment in this new cohort have classified the new diagnostic criteria as based on weak evidence by the World Health Organization(62). There is question into the clinical significance of the outcomes such as neonatal c-peptide of which the diagnostic criteria is based upon(79). Also there are concerns regarding the ability of the health system to cope with the potential increase in women diagnosed with GDM with many health areas reporting a significant increase in the incidence of GDM following the new diagnostic criteria (87). Furthermore, has progressive emphasis on tightening the glycaemic level both in diagnosis and management created a tunnel vision in the overall pregnancy care when evidence has shown that factors such as obesity have an equal if not greater influence on adverse maternal and foetal outcome when it was examined in the same HAPO study sample(119).

To examine the impact of adopting the new criteria for GDM, we conducted a retrospective cohort study into the pregnancy outcomes of a population of ethnically diverse women from a catchment of the Western Sydney area.

### 3.2 Aims:

- To compare the risk of adverse pregnancy outcomes between women without GDM with women with treated GDM (based on the old ADIPS1998 criteria) as well as untreated women who would have been newly classified as GDM under the new IADPSG 2010 criteria.
- To determine independent risk factors for adverse pregnancy outcomes via multivariate analysis.
- To examine the characteristics of women diagnosed as GDM under the new IADPSG 2010 criteria.
- To explore the impact of BMI on the risk of adverse pregnancy outcomes particularly with respect to the women who would be newly classified as GDM under the IADPSG 2010 criteria.
3.3 Methods

3.3.1 Ethics Approval

Ethics Approval was gained from the Western Sydney Local Health District Human Research Ethics Committee HREC (4037) LNR/14/WMEAD/236, SSA LNRSSA/14/WMEAD262.

3.3.2 Study Sample Selection

We conducted a retrospective cohort study on all women over a 5 year period satisfying the following inclusion criteria

- singleton pregnancy
- antenatal 75g oral glucose tolerance test (OGTT) performed at Westmead Hospital due to a positive 50g oral glucose challenge (GCT) or presence of risk factors.
- no history of pre-gestational diabetes
- delivery at >24 weeks gestation at Westmead Hospital between 01/01/2011 and 16/04/2015.

Only the first pregnancy was used for analysis if a woman has had multiple pregnancies during this period. The fasting and 2 hour oral glucose tolerance test (OGTT) results were obtained from the Westmead Hospital Biochemistry Laboratory database 2011 - 2015. Information on the women’s ethnic demography based on country of birth (Table 6), pre-gestational body mass index (BMI) by recall (or if unavailable BMI at first booking), mode of delivery, gestation of delivery, neonatal birthweight and neonatal complications were obtained from the Westmead Hospital 2011 – 2015 Obstetrix database. Data linkage was performed between the OGTT database and the Obstetrix database to match each woman’s antenatal OGTT with the corresponding pregnancy outcome.
Table 6: Countries in Ethnicity Grouping

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<td>United Arab Emirates</td>
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<td>USA</td>
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3.3.3 GDM screening, Diagnosis and Management

3.3.3a GDM Screening

All women reaching 26 – 28 weeks gestation who have antenatal care at Westmead Hospital were given a 50g GCT whereby a capillary blood glucose level was measured via a peripheral glucometer (Optium Xceed meter from 2011 - 2014, and the StatStrip Xpress glucometer from 2014-2015) 1 hour post ingestion of a 50g glucose load. Generally only those whose 1hour result ≥7.8mmol/L were referred to have a 2 sample 75g OGTT. A modest number may have gone direct to a 75g OGTT if they had early testing for GDM because of previous GDM, or on the basis of a clinical decision. The 2 sample 75g oral glucose tolerance test was performed by measuring the plasma blood glucose levels (Ortho-Clinical Diagnostics Fusion 5.1 testing system 2012 – 2014, the Siemens Dimension Vista 1500 Analyser 2014 – 2015) from peripheral venous blood sampling at fasting, and 2 hours post ingestion of a 75g glucose load.

3.3.3b GDM Management Protocol

At the time of the study, the diagnosis of GDM and referral for subsequent management at Westmead Hospital was based on the ADIPS 1998 criteria. Based on the results of the 75g OGTT, women whose fasting result was ≥5.5mmol/L and/or 2hour result ≥8.0mmol/L were given hyperglycaemia management via a combination of lifestyle, dietary advice and insulin therapy by a team consisting of midwives, dieticians, diabetic educators, obstetricians and endocrinologists. The target for management aimed for a fasting blood glucose level of <5.5 mmol/L and 2 hour post prandial blood glucose level <7.0mmol/L.

3.3.4 Cohort Allocation

Women who fulfilled the inclusion criteria for the study were divided into 4 cohorts. (Figure 3). The control cohort consisted women who did not have GDM under any diagnostic criteria based on their 75g OGTT (fasting BGL<5.1 and 2 hour BGL<8.0). The ‘GDM2010 Only’ group consisted of women who would be diagnosed with GDM under the new IADPSG 2010 criteria only, but did not satisfy the ADIPS 1998 criteria (fasting BGL5.1-5.4mmol/L and 2hr BGL <8.0mmol/L). These women were not managed for GDM during their pregnancy. The
‘GDM1998 Only’ group consisted of women who were diagnosed with GDM under the ADIPS 1998 criteria only but did not satisfy the IADPSG 2010 criteria (fasting BGL<5.1mmol/L and 2 hr BGL 8-8.4mmol/L). The ‘GDM Both’ group consisted of women who satisfied both the IADPSG 2010 and ADIPS 1998 criteria of GDM (fasting BGL≥5.5mmol/L and/or 2hr BGL≥8.5mmol/L, or fasting BGL≥5.1mmol/L and 2hr BGL≥8.0mmol/L). Both the ‘GDM1998 Only’ and ‘GDM both’ cohorts were given GDM management as per the Westmead Hospital protocol. It is recognised that because only a 2 sample GTT was performed as it was the hospital protocol at the time, there are some women who would have GDM under the IADPSG 2010 criteria on the basis of the one hour sample only who were assigned into the control group.

Figure 3: Gestational Diabetes Cohort Allocation

3.3.5 Outcome Measures

The outcomes examined were large for gestation, small for gestation, preterm delivery, primary caesarean section, shoulder dystocia and neonatal stillbirth. The maternal BMI was pre-gestational BMI via recall or if unavailable, the measured BMI at the time of first booking into the Westmead Hospital antenatal review. The neonatal birth centile was calculated via a customized centile calculator (201) adjusting for maternal age, parity, ethnicity, neonatal sex, gestation and weight. Small for gestational age was classified as <10th neonatal birth centile. Large for gestational age was classified as >90th neonatal birth centile. Preterm birth was classified as delivery at <37 weeks gestation. The application of McRobert’s Manoeuvre documented in the Obstetrix database was utilized as an indicator of
the presence of shoulder dystocia. The outcome of primary caesarean section was analysed in women who have not had a previous caesarean section or major uterine surgery in order to negate confounders such as the need of a caesarean section due to a previous uterine scar. Both univariate and multivariate analyses were performed to assess for independent risk factors of the outcome measures. Multivariate analyses were adjusted for GDM cohort, BMI category and smoking status. BMI categories were based on the Institute of Medicine classification with underweight BMI <18.5, normal BMI 18.5-24.9, overweight BMI 25-29.9 and obese BMI ≥30.

3.3.6 Secondary Analysis

A secondary analysis was performed on the women untreated for GDM (no GDM group and GDM2010 Only group) by allocating their pre-gestational (if unavailable, 1st antenatal review) BMI into categories based on the Institute of Medicine BMI classification. Restricting the secondary analysis to only these untreated women, allows an assessment of the influence of obesity and other risk factors without being confounded by the effects of treatment. Furthermore it is important to analyse these 2 cohorts as a change in diagnostic criteria which would result in diabetes treatment being administered to some of these women needs to be justified on the basis of local data. Outcome measures include LGA, SGA, preterm delivery, shoulder dystocia, primary caesarean section and stillbirth. By selecting only the untreated women, we aimed to eliminate the confounding weight management effect of GDM treatment to examine exclusively the effect of BMI on adverse pregnancy outcomes in women who would not be diagnosed with GDM under the ADIPS 1998 criteria.

3.3.7 Statistical Analysis

Statistical analysis was performed using SPSS version 23. Significance was set at p-value<0.05 using a 2 tailed test. Parametric data was reported as means and standard deviations. Non-parametric data was reported as median and interquartile range. Comparison of multiple parametric and non-parametric continuous data was performed via ANOVA or the Kruskal-Wallis test respectively. Comparisons of categorical data was performed using the Pearson Chi-Square. Logistic and multiple regression models were utilized for multivariate analysis.
3.4 Results

From January 2011 to 15th April 2015, 4081 women without pre-gestational diabetes underwent a 75g OGTT at Westmead Hospital during pregnancy and subsequently had a singleton delivery at Westmead Hospital>24 weeks gestation. In our study population, 78% (3185) of women had no GDM, 2.3% (94) of women had GDM via IADPSG 2010 criteria only, 5.4% (221) of women had GDM via ADIPS 1998 criteria only, and 14.2% (581) had GDM satisfying both criteria.

The baseline characteristics are shown in Table 7. Women in the ‘GDM2010 Only’ cohort compared to the ‘GDM1998 ONLY’ cohort had a significantly higher proportion of obesity (29.0% vs 8.2%), higher proportion of subcontinental ethnicity (44.7% vs 29.0%), and lower proportion of East and Southeast Asian ethnicity (8.5% vs 33.9%). In addition, there was a high prevalence of diabetes in the family history of women with GDM compared to those without GDM (control 36.9% vs GDM2010 only 45.7%, GDM1998 only 44.2%, GDM both 53.5%).
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Control</th>
<th>GDM2010 Only</th>
<th>GDM1998 Only</th>
<th>GDM Both</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort numbers</td>
<td>3185 (78%)</td>
<td>94 (2.3%)</td>
<td>221 (5.4%)</td>
<td>581 (14.2%)</td>
<td></td>
</tr>
<tr>
<td>Maternal age*</td>
<td>30.0 (27 – 33)</td>
<td>30.5 (27 - 34)</td>
<td>31.0 (28 – 34)</td>
<td>31 (27.5 - 34.5)</td>
<td>&lt;0.001</td>
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<tr>
<td>Maternal BMI *</td>
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<tr>
<td></td>
<td>Normal</td>
<td>23.44 (20.27 – 26.62)</td>
<td>25.78 (21.71 - 29.85)</td>
<td>23.07 (20.45 – 25.70)</td>
<td>24.51 (21.33 – 27.70)</td>
</tr>
<tr>
<td></td>
<td>Underweight</td>
<td>55.2% (1747)</td>
<td>44.1% (41)</td>
<td>60.5% (133)</td>
<td>49.5% (284)</td>
</tr>
<tr>
<td></td>
<td>Overweight</td>
<td>7.1% (226)</td>
<td>2.2% (2)</td>
<td>8.2% (18)</td>
<td>3.8% (22)</td>
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<tr>
<td></td>
<td>Obese</td>
<td>22.5% (711)</td>
<td>24.7% (23)</td>
<td>23.2% (51)</td>
<td>28.4% (163)</td>
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<tr>
<td></td>
<td></td>
<td>15.2% (480)</td>
<td>29.0% (27)</td>
<td>8.2% (18)</td>
<td>18.3% (105)</td>
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<tr>
<td>Ethnicity</td>
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<td></td>
<td>Caucasians</td>
<td>45.1% (1435)</td>
<td>37.2% (35)</td>
<td>31.7% (70)</td>
<td>29.8% (173)</td>
</tr>
<tr>
<td></td>
<td>Subcontinental</td>
<td>27.7% (882)</td>
<td>44.7% (42)</td>
<td>29.0% (64)</td>
<td>39.1% (227)</td>
</tr>
<tr>
<td></td>
<td>East and Southeast Asian</td>
<td>18.5% (590)</td>
<td>8.5% (8)</td>
<td>33.9% (75)</td>
<td>23.2% (135)</td>
</tr>
<tr>
<td></td>
<td>African</td>
<td>3.5% (112)</td>
<td>4.3% (4)</td>
<td>1.8% (4)</td>
<td>2.4% (14)</td>
</tr>
<tr>
<td></td>
<td>South American</td>
<td>1.2% (38)</td>
<td>1.1% (1)</td>
<td>0.9% (2)</td>
<td>1.0% (6)</td>
</tr>
<tr>
<td></td>
<td>Polynesian</td>
<td>4.0% (126)</td>
<td>4.3% (4)</td>
<td>2.7% (6)</td>
<td>4.5% (26)</td>
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<tr>
<td>Plasma glucose</td>
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<tr>
<td></td>
<td>Fasting*</td>
<td>4.20 (3.25 – 5.15)</td>
<td>5.2 (5.1 – 5.3)</td>
<td>4.2 (3.95 – 4.45)</td>
<td>4.7 (4.15 – 5.25)</td>
</tr>
<tr>
<td></td>
<td>2hours*</td>
<td>6.1 (5.35 – 6.85)</td>
<td>6.6 (5.95 – 7.25)</td>
<td>8.2 (8.05 – 8.35)</td>
<td>9.1 (8.45 – 9.75)</td>
</tr>
<tr>
<td>Smoking in pregnancy</td>
<td></td>
<td>5.8% (186)</td>
<td>3.2% (3)</td>
<td>3.2% (7)</td>
<td>3.8% (22)</td>
</tr>
<tr>
<td>Family history of Diabetes</td>
<td></td>
<td>36.9% (1169)</td>
<td>45.7% (43)</td>
<td>44.2% (96)</td>
<td>53.5% (576)</td>
</tr>
</tbody>
</table>

*median and interquartile range

Column proportions used.
3.4.1 GDM Diagnostic Criteria and Adverse Outcomes

Table 8 shows the results of univariate and multivariate comparisons between the three GDM cohorts and control, with respect to the adverse outcomes of LGA, SGA, preterm delivery, shoulder dystocia and primary caesarean section between. Women in the untreated ‘GDM2010 Only’ cohort had an increased risk of LGA (20.2% vs 9.4%, OR=2.45, 95%CI 1.46 – 4.12, p=0.001) and primary caesarean section (33.8% vs 20.1%, OR=2.03, 95% CI 1.23 – 3.35, p=0.006), decreased risk of SGA (8.5% vs 17.2%, OR=0.45, 95%CI 0.22 – 0.93, p=0.03) compared to control. On multivariable analysis after adjusting for pre-pregnancy BMI and smoking status, the risk for LGA remained significantly increased in this cohort (OR 1.91, 95%CI 1.11 – 3.31, p=0.02). The risk of primary caesarean section also remained increased (OR 1.92, 95%CI 1.15 – 3.18, p=0.01).

Women in the treated ‘GDM1998 Only’ cohort had a decreased risk of LGA (2.7% vs 9.4%, OR=0.27, 95%CI 0.12 – 0.61, p=0.002) compared to control. This cohort also had an increased risk of SGA (24.4% vs 17.2%, OR=1.56, 95% CI 1.13 – 2.14, p=0.007) compared to control. Both remained significant on multivariable analysis with the adjusted LGA OR=0.32 (95%CI 0.14 – 0.72, p=0.006), and adjusted SGA OR=1.49 (95%CI 1.07 – 2.06, p=0.02).

Women in the treated ‘GDM Both’ cohort had an increased risk in primary caesarean section (24.5% vs 20.1%, OR=1.29, 95%CI 1.02 – 1.62, p=0.03), which became insignificant after adjustment for BMI status and smoking status on multivariable analysis (OR=1.25, 95%CI 0.99 – 1.58, p=0.06).

There was insufficient occurrence of neonatal stillbirth for meaningful analysis of this outcome in any of the cohorts.
Table 8: Adverse Pregnancy Outcomes in GDM Cohorts

<table>
<thead>
<tr>
<th>Adverse Pregnancy Outcomes</th>
<th>Control</th>
<th>GDM2010 Only</th>
<th>GDM1998 Only</th>
<th>GDM Both</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Proportion</td>
<td>Proportion</td>
<td>Univariate Odds Ratio</td>
<td>Multivariate Odds Ratio</td>
</tr>
<tr>
<td>LGA N₁=4080 N²=4046</td>
<td>9.4% (298)</td>
<td>20.2% (19)</td>
<td>2.45 (1.46 – 4.12) p=0.001</td>
<td>1.91 (1.11 – 3.31) p=0.02</td>
</tr>
<tr>
<td>SGA N₁=4080 N²=4046</td>
<td>17.2% (548)</td>
<td>8.5% (8)</td>
<td>0.45 (0.22 – 0.93) p=0.03</td>
<td>0.51 (0.25 – 1.06) p=0.07</td>
</tr>
<tr>
<td>Preterm delivery N₁=4081 N²=4047</td>
<td>5.6% (178)</td>
<td>4.3% (4)</td>
<td>0.75 (0.27 – 2.07) p=0.58</td>
<td>0.76 (0.27 – 2.09) p=0.59</td>
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<tr>
<td>Shoulder dystocia N₁=4081 N²=4047</td>
<td>6.8% (215)</td>
<td>5.3% (5)</td>
<td>0.78 (0.31 – 1.93) p=0.59</td>
<td>0.57 (0.21 – 1.58) p=0.28</td>
</tr>
<tr>
<td>Primary caesarean section N₁=3376 N²=3349</td>
<td>20.1% (536)</td>
<td>33.8% (24)</td>
<td>2.03 (1.23 – 3.35) p=0.006</td>
<td>1.92 (1.15 – 3.18) p=0.01</td>
</tr>
<tr>
<td>Stillbirth N₁=4081 N²=4047</td>
<td>0.3% (8)</td>
<td>0.0% (0)</td>
<td>0.0% (0)</td>
<td>0.3% (2)</td>
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N₁ – sample size for univariable analysis
N² – sample size for multivariable analysis
Column Proportions used.
Multivariable analysis adjusted for BMI category and smoking status.
3.4.2 Maternal BMI and Adverse Outcomes

Table 9 shows the results of univariate and multivariate BMI analysis of the entire study sample. Compared to women within the normal BMI range, overweight and obese women had increased risk of LGA (overweight OR 1.86, 95%CI 1.41 – 2.44, p<0.001; obese OR=4.43, 95%CI 3.41 – 5.74, p<0.001), and shoulder dystocia (overweight OR 1.67, 95%CI 1.24 – 2.25, p=0.001; obese OR 1.62, 95%CI 1.15 – 2.28, p=0.01). Only women within the obese BMI range had an increased risk of primary caesarean section (OR=1.69, 95%CI 1.35 – 2.12, p<0.001). All these risks remained significant on multivariate analysis for LGA (overweight OR 1.84, 95%CI 1.40 – 2.43, p<0.001; obese OR 4.31, 95%CI 3.31 – 5.60, p<0.001), shoulder dystocia (overweight OR=1.68, 95%CI 1.25 – 2.27, p=0.001; obese OR=1.61, 95%CI 1.14 – 2.28, p=0.01), and primary caesarean section (obese OR=1.68, 95%CI 1.33 – 2.11, p<0.001). Both women in the overweight and obese BMI range had decreased risk of SGA on both univariate and multivariate analysis (overweight univariate OR=0.69, 95%CI 0.56 – 0.85, p=0.001, multivariate OR=0.69, 95%CI 0.56 – 0.85, p<0.001; obese univariate OR=0.46, 95%CI 0.35 – 0.61, p<0.001, multivariable OR=0.45, 95%CI 0.34 – 0.60, p<0.001).

Women in the underweight BMI range had decreased risk of LGA and primary caesarean section on both univariate and multivariate analysis (LGA univariate OR=0.43, 95%CI 0.20 – 0.93, p=0.03, multivariate OR=0.44, 95%CI 0.20 – 0.95, p=0.04; primary caesarean section univariate OR=0.65, 95%CI 0.44 – 0.95, p=0.02, multivariate OR=0.66, 95%CI 0.45 – 0.96, p=0.03). Based on the multivariate analysis, smoking was an independent risk factor for SGA (OR=1.71, 95%CI 1.22 – 2.38, p=0.002).
Table 9: Adverse pregnancy outcomes in BMI categories in entire study sample

<table>
<thead>
<tr>
<th>Adverse Outcomes</th>
<th>Normal</th>
<th>Underweight</th>
<th>Overweight</th>
<th>Multivariate</th>
<th>Obese</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Proportion</td>
<td>Proportion</td>
<td>Univariate Odds Ratio</td>
<td>Proportion</td>
<td>Univariate Odds Ratio</td>
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<tr>
<td>LGA</td>
<td>5.9% (129)</td>
<td>2.6% (7)</td>
<td>0.43 (0.20 – 0.93) p=0.03</td>
<td>0.44 (0.20 – 0.95) p=0.04</td>
<td>10.3% (98)</td>
<td>1.86 (1.41 – 2.44) p&lt;0.001</td>
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<td>20.1% (444)</td>
<td>22.0% (59)</td>
<td>1.12 (0.82 – 1.52) p=0.47</td>
<td>1.12 (0.83 – 1.53) p=0.46</td>
<td>14.9% (141)</td>
<td>0.69 (0.56 – 0.85) p&lt;0.001</td>
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<td></td>
<td>5.7% (126)</td>
<td>4.5% (12)</td>
<td>0.77 (0.42 – 1.42) p=0.41</td>
<td>0.79 (0.43 – 1.44) p=0.43</td>
<td>5.6% (53)</td>
<td>0.98 (0.70 – 1.36) p=0.89</td>
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<td></td>
<td>5.2% (114)</td>
<td>4.9% (13)</td>
<td>0.94 (0.52 – 1.68) p=0.83</td>
<td>0.92 (0.51 – 1.66) p=0.79</td>
<td>8.3% (79)</td>
<td>1.67 (1.24 – 2.25) p=0.001</td>
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<tr>
<td></td>
<td>19.9% (375)</td>
<td>13.8% (34)</td>
<td>0.65 (0.44 – 0.95) p=0.02</td>
<td>0.66 (0.45 – 0.96) p=0.03</td>
<td>21.2% (158)</td>
<td>1.09 (0.88 – 1.34) p=0.49</td>
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<tr>
<td></td>
<td>0.1% (3)</td>
<td>0.4% (1)</td>
<td>2.75 (0.29 – 26.52) p=0.38</td>
<td>2.80 (0.29 – 27.11) p=0.37</td>
<td>0.5% (5)</td>
<td>3.89 (0.93 – 16.32) p=0.06</td>
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</tbody>
</table>

N¹ – sample size for univariate analysis
N² – sample size for multivariate analysis
Column Proportions used.
Multivariable analysis adjusted GDM status and smoking status.
3.4.3 Stratified Analysis of Maternal BMI and Adverse Outcomes

Given that the entire study sample included women who were both treated and untreated for GDM, we restricted our further analysis to include only the untreated women (the control cohort and the ‘GDM2010 only’ cohort) to assess the independent risk imposed by BMI without the confounder of any effect GDM treatment may have had on the risk of BMI. This is important as part of the controversy with the new IADPSG criteria is whether we should be labelling these extra women on the mild end of the spectrum and treating them for GDM.

One of our aims is to determine if obesity is a greater issue. Table 10 shows the odds ratios of the BMI categories on adverse pregnancy outcomes in a univariate and a multivariate model adjusted for GDM and smoking status.

The results of the subanalysis are very similar to the analysis of the entire cohort. On both the univariate and multivariate models, women in the overweight and obese range BMI remained at increased risk of LGA (overweight univariate OR=1.86, 95%CI 1.38 – 2.51, p<0.001; multivariate OR=1.86, 95%CI 1.38 – 2.51, p<0.001; obese univariate OR=3.82, 95%CI 2.87 – 5.10 p<0.001, multivariate OR=3.85, 95%CI 2.89 – 5.15, p<0.001). Risk of shoulder dystocia was also increased in the univariate and multivariate models for the overweight and obese cohorts (overweight univariate OR=1.74, 95%CI 1.26 – 2.40, p=0.001; multivariate OR=1.75, 95%CI 1.27 – 2.41, p=0.001; obese univariate OR=1.50, 95%CI 1.03 – 2.19, p=0.04; multivariate OR=1.51, 95%CI 1.03 – 2.21, p=0.03). Only the obese cohort had high risk of primary caesarean section (univariate OR=1.63, 95%CI 1.26 – 2.10, p<0.001; multivariate OR=1.63, 95%CI 1.26 – 2.10, p<0.001). However in the overweight and obese cohorts there was a decreased risk of SGA (overweight univariate OR=0.76, 95%CI 0.60 – 0.96, p=0.02; multivariate OR=0.75, 95%CI 0.59 – 0.95, p=0.02; obese OR=0.50, 95%CI 0.37 – 0.68, p<0.001; multivariate OR=0.48, 95%CI 0.35 – 0.65, p<0.001). Women in the underweight cohort were again demonstrated to have lower risk of LGA (univariate OR=0.33, 95%CI 0.13 – 0.82, p=0.03; multivariate OR=0.34, 95%CI 0.14 – 0.83, p=0.02), and primary caesarean section (univariate OR=0.57, 95%CI 0.37 – 0.88, p=0.01; multivariate OR=0.57, 95%CI 0.37 – 0.88, p=0.01). In the multivariate model of untreated women, the GDM2010 only cohort was shown to be an independent risk factor for LGA (OR=1.92, 95%CI 1.12 – 3.32, p=0.02) and primary caesarean section (OR=1.91, 95%CI 1.15 – 3.18, p=0.01). Smoking was again shown to be an independent risk factor of SGA (OR=1.75, 95%CI 1.23 – 2.15, p=0.002).
Table 10: Adverse Pregnancy Outcomes in BMI Categories in Untreated Women

<table>
<thead>
<tr>
<th>Adverse Outcomes</th>
<th>Normal N=1788</th>
<th>Underweight N=228</th>
<th>Overweight N=734</th>
<th>Obese N=507</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Proportion</td>
<td>Proportion</td>
<td>Odds Ratio</td>
<td>Proportion</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>univariate</td>
<td></td>
</tr>
<tr>
<td>LGA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=3256 N=3255</td>
<td>6.3% (113)</td>
<td>2.2% (5)</td>
<td>0.33 (0.13 – 0.82) p=0.02</td>
<td>0.34 (0.14 – 0.83) p=0.02</td>
</tr>
<tr>
<td>SGA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=3256 N=3255</td>
<td>18.9% (338)</td>
<td>23.7% (54)</td>
<td>1.33 (0.96 – 1.85) p=0.09</td>
<td>1.33 (0.96 – 1.85) p=0.09</td>
</tr>
<tr>
<td>Preterm delivery</td>
<td>5.2% (93)</td>
<td>4.4% (10)</td>
<td>0.84 (0.43 – 1.63) p=0.60</td>
<td>0.84 (0.43 – 1.63) p=0.60</td>
</tr>
<tr>
<td>Shoulder dystocia</td>
<td>5.5% (99)</td>
<td>4.4% (10)</td>
<td>0.78 (0.40 – 1.52) p=0.47</td>
<td>0.78 (0.40 – 1.52) p=0.46</td>
</tr>
<tr>
<td>Primary caesarean</td>
<td>19.7% (303)</td>
<td>12.3% (26)</td>
<td>0.57 (0.37 – 0.88) p=0.01</td>
<td>0.57 (0.37 – 0.88) p=0.01</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>0.2% (3)</td>
<td>0.4% (1)</td>
<td>2.62 (0.27 – 25.31) p=0.41</td>
<td>2.62 (0.27 – 25.29) p=0.41</td>
</tr>
</tbody>
</table>

N¹ – sample size for univariate analysis
N² – sample size for multivariate analysis
Column Proportions used.
Multivariate analysis adjusted for GDM status and smoking status
3.5 Discussion

3.5.1 Higher Pregnancy Adverse Outcomes with GDM 2010 only Cohort

We have found that untreated women in the ‘GDM 2010 only’ cohort who met the new IADPSG 2010 criteria for GDM but not the old ADIPS 1998 criteria for GDM have an increased risk of LGA and primary caesarean section compared to non-GDM patients. The risks remained significant after adjustment for maternal pre-gestational BMI, indicating that a mildly elevated fasting BGL with a lower post glucose load BGL within the new GDM diagnostic range is an independent risk factor for these adverse pregnancy outcomes. The odds ratio of 2.45 for the development of LGA, and the odds ratio of 2.03 for caesarean section in the ‘GDM 2010 only’ cohort of our study are both higher than the odds ratio of 1.75 set by the IADPSG in formulation of the new GDM diagnostic criteria based on the HAPO study, albeit the IADPSG used a combined odds ratio of LGA, caesarean section, and 2 other adverse outcomes. Therefore, we did find that the group of women diagnosed via the IADPSG2010 criteria previously not encompassed in the ADIPS1998 criteria have a higher risk of adverse pregnancy outcomes consistent with, if not more than, the rate demonstrated by the HAPO data.

3.5.2 Adverse Pregnancy Outcomes in Treated GDM

The absence of significant risk of LGA in the cohorts treated for GDM compared to control group is suggestive of the beneficial effect of treatment in improving the outcome of LGA, in particularly the ‘GDM both’ cohort which in our study represented those with the most severe impairment of glycaemic homeostasis. However, as our study is retrospective observational in nature, we cannot be certain that the reduction in LGA is entirely due to the intervention.

The persisting higher risk of primary caesarean section in the ‘GDM both’ cohort despite treatment and the absence of LGA highlights the multifaceted pathophysiology of GDM. A treatment based on lowering of the maternal BGL did not appear to completely ameliorate the risk of the need for caesarean section, which could be due to either the treatment target used or achieved was not adequate enough, or that there were other aspects in the pathophysiology of GDM as a condition other than the maternal glucose that imparts the adverse risks. As
primary caesarean section was utilized as a surrogate marker of the presence of other adverse maternal and foetal pregnancy events such as pre-eclampsia, placental praevia, foetal distress, future studies examining the risk of these outcomes in women with treated and untreated GDM would assist with answering this question. Another possibility is that the labelling of the woman as having GDM lowers the threshold for performing a caesarean section. Similarly, in the Atlantic Diabetes in Pregnancy Study (202), the increased rate of caesarean section in women with GDM was mostly due to elective caesarean procedures.

Concerningly, women in the ‘GDM 1998 only’ who had GDM by the 1998 ADIPS criteria alone were found to have an increased rate of SGA and this is the first study to have observed this outcome. In this group of women, it was also found that their rate of LGA was even lower than the control, suggesting a generalized decrease in the neonatal birthweight. Given that SGA was historically not an adverse pregnancy effect traditionally associated with GDM, we may infer this as a potential outcome of treatment in this cohort. Plausible explanation for this include over treatment in this group of women. It is possible that some of these women over-restricted their dietary intake, or perhaps glucose control was excessively tight, leading to reduced passive diffusion of maternal glucose across the placenta for foetal growth and reduced growth hormone effect from the resultant decrease in foetal insulin secretion. This issue challenges the appropriateness of utilizing the ADIPS1998 criteria for diagnosis and treatment of GDM. As the ADIPS 1998 diagnostic criteria was derived from statistical distribution of maternal glucose data rather than outcome data of adverse events, the baseline risk of these women to the adverse pregnancy outcomes if untreated have not previously been determined, therefore the evidence for treatment in these women were never established. In addition, despite the risk of adverse pregnancy outcomes being continuous with the maternal OGTT levels at diagnosis, the management target for these women is based on the assumption that there is a threshold value of maternal BGL above which there may be the development of adverse pregnancy events. Thus the surprising finding of increase in SGA in this cohort brings up three important points regarding recommendation for the implementation of interventions. Firstly, the baseline risk of the adverse outcome in a well-defined target population needs to be established. Secondly, evidence of the relative benefit and risks of the treatment should be demonstrated. Thirdly, the relative benefit of a universal treatment target may need to be examined in multiple cohorts when the risk of the adverse outcome is associated with maternal 75g OGTT results in a linearly continuous pattern.
3.5.3 Shifting Demographics of the GDM Population

Based on our study population, it appears that the new GDM criteria will herald a change in the demographics in the women being managed for GDM. Based on the ethnicity distribution across the cohort groups, there was a significant higher proportion of women from subcontinental background in the ‘GDM 2010 only’ cohort (44.7%) compared to ‘GDM 1998 only’ cohort (29.0%) suggesting that these women have a higher propensity for mildly elevated fasting BGL. This is concordant with data from studies in India utilizing the IADPSG 2010 criteria which showed not only a significant increase in prevalence of GDM in the Indian population of up to 41% (203), but also that up to 94% of the women were diagnosed on the fasting BGL level alone (204). Such a high prevalence of almost half of pregnant women in a particular ethnic group being diagnosed with a pathology is highly alarming, yet there is a paucity of studies on whether the same adverse pregnancy risks apply to these women of subcontinental ethnicity as there were no subcontinental centres involved in the HAPO study. Notably, the Diabetes in Pregnancy Study Group India uses the 2 hour result only, for the diagnosis of GDM, and does not collect a fasting sample (205). In our study it appeared that there would be a smaller proportion of women of East and Southeast Asian ethnicity being diagnosed with GDM under the new criteria, ‘GDM 2010 only’ (8.5%) vs ‘GDM 1998 only’ (33.9%), suggesting perhaps an increased susceptibility to post prandial hyperglycaemia. This may reflect the lower beta-islet cell function in East and Southeast Asians compared to Western Europeans as demonstrated in ethnicity studies on normal pregnant women (45). The decrease in diagnosis of GDM in the East and Southeast Asian population with the new diagnostic criteria is discordant with other studies which have all shown a rise in incidence (75, 206). It may be that in our study, a significant proportion of women of East and Southeast Asian background with potential GDM were filtered out by the 50g GCT or would have fallen in the 1 hour OGTT result which was not performed in our study. In light of the introduction of the new 2010 AIDPSG diagnostic criteria, there would be an associated shift in the ethnic distribution of women being managed for GDM. This may present as an issue because it is unknown whether ethnicity is a disease modifier of the adverse pregnancy outcomes, as the risk profiling in those most affected appears to be lacking, let alone any interventional data regarding the benefits of treatment. Hence further ethnic focused research in risk profiling is important to address this issue.
### 3.5.4 Adverse Pregnancy Outcomes in Obesity

In our analysis examining the impact of pre-gestational BMI on adverse pregnancy outcomes, we found that BMI in the overweight range and above was an independent risk factor for LGA and shoulder dystocia, while BMI in the obese range was an independent risk factor of primary caesarean section as well (Table 11).

Table 11: Comparison of Adverse Pregnancy Outcome in GDM2010 and Obesity Cohorts within the Untreated Women

| Adverse Pregnancy Outcome | Odds Ratio
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>GDM2010 only</td>
<td>Obesity</td>
</tr>
<tr>
<td>LGA</td>
<td>1.92 (1.12 – 3.32) p=0.02</td>
</tr>
<tr>
<td>SGA</td>
<td>0.51 (0.25 – 1.07) p=0.07</td>
</tr>
<tr>
<td>Preterm delivery</td>
<td>0.75 (0.27 – 2.06) p=0.57</td>
</tr>
<tr>
<td>Shoulder dystocia</td>
<td>0.57 (0.21 – 1.58) p=0.28</td>
</tr>
<tr>
<td>Caesarean section</td>
<td>1.91 (1.15 – 3.18) p=0.01</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>0</td>
</tr>
</tbody>
</table>

These risks are consistent with the BMI analysis from the HAPO cohort. The higher odds ratio of obesity compared to IADPSG 2010 Only GDM status signifies that obesity is a stronger risk factor for LGA than mild fasting hyperglycaemia. Risk factors for shoulder dystocia have previously been shown to be macrosomia, LGA, operative vaginal delivery or higher fasting maternal BGL (207). However, despite both having increased risk of LGA, only higher BMI and not the ‘GDM 2010 only’ cohort was associated with shoulder dystocia in our study. Apart from obesity itself being a true independent risk factor predisposing to development of shoulder dystocia, another possible explanation of this result could be that the ‘GDM 2010 only’ cohort had more primary caesarean section (33.8% vs 28.5% in obese group) hence never progressed to manifest shoulder dystocia.

Based on our study sample, the IADPSG 2010 GDM diagnostic criteria included more women within the obese BMI category compared to the ADIPS 1998 GDM diagnostic criteria, as 29% of the women in the ‘IADPSG 2010 only’ group were within the obese range whereas only 8.2% of the women in the ‘ADIPS 1998 only’ group were obese. As lifestyle education is an integral overlapping aspect of treatment of both GDM and obesity, from a
practical point of view it could be speculated that diagnosing GDM via the IADPSG 2010 criteria could effectively target a greater proportion of women with both the risk factors of GDM and obesity. Conversely, as demonstrated by the overlapping adverse outcomes between GDM and obesity itself, it is important for future evaluation of GDM treatment to delineate whether any change in pregnancy outcome with treatment is secondary to treatment of the GDM or obesity in order to accurately determine the true independent effect of treatment on each individual risk factor. The focus of the professional societies has been on the treatment of hyperglycaemia, with little attention paid to the management of obesity in pregnancy. In part this may be because the management of obesity is challenging and does not fit easily into the medical model of care. However, although trials of weight management in pregnancy have had mixed results, a recent Cochrane analysis found that combined diet and physical activity interventions resulted in less gestational weight gain, fewer caesarean sections, and less macrosomia amongst obese pregnant women (123). Yet the benefits of treating women with mild fasting hyperglycaemia alone is unclear. It must be remembered that although 2 large randomised controlled trials showed a reduction in adverse outcomes with treatment of GDM (73, 74), in both trials inclusion was based on fasting and post glucose load diagnostic levels higher than the current diagnostic criteria, and the majority of women in our “GDM 2010” cohort would not have met the entry criteria for these trials.

3.5.5 Study Limitation and Future Research Directions

Of the 4081 women in our study, 19.6% (n=802) had GDM diagnosed under the ADIPS 1998 criteria. According to our data, if the new IADPSG diagnostic criteria were to be utilised, 16.5% (n=675) of women would need to be managed as GDM. Contrary to other similar studies in the Australian population which have shown a substantial increase in the incidence of GDM with the new criteria (85-87), our data may appear to demonstrate a decrease in the incidence of GDM, however this was undoubtedly due to the selection bias introduced by the fact that only women who were positive on the 50g GCT were referred for a formal 75g OGTT. Thus, a significant proportion of women with potential high fasting BGL who may fall into the ‘GDM 2010 only’ cohort were not included in our study as they were never referred for a formal 75g OGTT. Furthermore, we did not collect one hour BGLs on the GTT and therefore we are unable to identify patients who may have exceeded the one hour cut-off
or their contribution towards the incidence of GDM and their adverse pregnancy outcome risk profile.

An element of selection bias may also be present in our control group. Given that the 75g OGTT was generally only offered to women who have had a positive 50g GCT based on hospital screening policy, the control group in our study consisted of women who have had a positive 50g GCT therefore may be more carbohydrate intolerant with a different pregnancy risk profile compared to women who were negative on 50g GCT, despite both being GDM negative based on diagnostic thresholds.

In our multivariate model of the entire study cohort, we included BMI category as a cofactor. Given that treatment of GDM includes components of lifestyle management which may impact on both GDM and BMI, this creates an issue of confounding in our analysis. However, given the strong influence of BMI on pregnancy outcomes, it was important to include into our model. In addition we attempted to address this issue by performing a secondary analysis in only untreated women which was able to demonstrate the same result, to verify the validity of the strong effect high BMI confers on adverse pregnancy outcome in the original model. Given the adverse pregnancy risks conferred by increasing gestational weight gain(120-122), it would have been valuable to include this risk factor as part of the multivariable model, however this information was unavailable for analysis. Finally, as this was an observational study, the associations may only be interpreted as hypothesis generating rather than causal.

It is also important to remember that the IADPSG GDM diagnostic criteria have been based on the risk of immediate pregnancy outcomes without encompassing the long term risks of maternal development of type 2 diabetes(93), or risk of future glucose intolerance and obesity in the child(105, 108, 109). Therefore, we suggest that ethnic variations in GDM, interventional outcome trials and long term longitudinal studies are areas needing further research in order to redefine the risks and benefits of treatment.

### 3.6 Study Conclusion

Our study has shown an increased risk of LGA and primary caesarean section in women with untreated GDM via the new IADPSG diagnostic criteria. Our findings therefore indicate that treatment of the additional women diagnosed to have GDM alone by the IADPSG criteria is
justifiable because of their increased risk. We also demonstrated the potential efficacy of GDM treatment, with treated women with GDM under the 1998 ADIPS criteria achieving similar pregnancy outcomes to controls without GDM in our institution. However, we also demonstrated that obesity is a significant independent risk factor in causing adverse pregnancy outcomes with risk similar if not higher than that posed by GDM. This raises the question as to whether it is appropriate for hyperglycaemia to be the main concern in women with mild hyperglycaemia such as in the IADPSG 2010 Only group, or is it obesity that we should really be targeting?
4. The Effect of Antepartum and Intrapartum Glycaemic Control on Neonatal Hypoglycaemia in Women with Pre-gestational Diabetes

4.1 Introduction

Transient neonatal hypoglycaemia is a phenomenon surrounded by controversy regarding its diagnosis due to the competing evidence regarding its pathological impact. Whilst the adverse effect of severe symptomatic hypoglycaemia is more evident, obscurity surrounds issues such as the transition point between physiological versus pathological asymptomatic neonatal hypoglycaemia, the ability of the neonatal brain to adapt in mild hypoglycaemic states, and the short term as well as long term impact of mild neonatal hypoglycaemia. A graded treatment plan is often adopted with breast and formula feeding utilized in mild hypoglycaemia between 2.2 – 2.5mmol/L, whilst severe hypoglycaemia is treated with IV dextrose. Intensive monitoring often takes place in the neonatal ICU setting and this creates anxiety for the parents, prevents early maternal neonatal bonding, and an increase in resource requirement for the healthcare system.

A comprehensive understanding of risk factors is not only crucial in effective resource allocation in pre-empting neonates likely to develop hypoglycaemia but also identifying modifiable factors to prevent its onset. Neonates of diabetic mothers, including gestational diabetes, have an increased incidence of neonatal hypoglycaemia of up to 70%,(147) compared to the incidence of 10% in termed neonates of healthy mothers (140). The pathophysiology of this increased risk is thought to be due to in utero priming of the neonate to higher maternal BGL resulting in foetal hyperinsulinaemia. Hence when the maternal supply via the umbilical cord is removed post-delivery, the persistence of hyperinsulinaemia without a continuous glucose supply results in the hypoglycaemia (149). This hypothesis is further consolidated by evidence of higher cord c-peptide in hyperglycaemic pregnancy (1). Predictive studies seeking to identify modifiable factors that impart increasing risk of neonatal hypoglycaemia in this population have more consistently shown that preterm birth (138, 167, 208) and neonatal large for gestation (146, 208) to be significant risk factors.
For women with insulin-requiring diabetes in pregnancy, the intrapartum period of delivery is usually intensively monitored and controlled due to the high risk of adverse pregnancy outcomes associated with diabetes mellitus and the culture of hospital based delivery universally in all pregnancy. Hence, risk factors for neonatal hypoglycaemia that arise during this period may potentially be modifiable and practically achievable in a health care setting, yet there has not been consistent evidence nor studies comprehensively investigating the various aspects of intrapartum glycaemic control on neonatal hypoglycaemia for women with diabetes. This confusion is further exacerbated by the paucity of literature available exploring the role of glycaemic control factors such as maternal insulin use(147, 194) and antepartum Hba1c(195) in neonatal hypoglycaemia. There is even less available data examining aspects of intrapartum glycaemic control (187-189). In addition, difficulty with interpreting these studies include heterogeneity of diagnostic criteria used to define neonatal hypoglycaemia, study population consisting of a mix of GDM and pre-gestation diabetes women, different exclusion criteria for preterm neonates and different or lack of variables used for adjustment in regression analysis.

4.2 Aims

Our study is aimed at examining the association between intrapartum glycaemic control in women with insulin-requiring pre-gestational diabetes and the outcome of neonatal hypoglycaemia to expand our understanding on modifiable risk factors in reducing the incidence of neonatal hypoglycaemia in women with diabetes. In addition the study aims to determine relative contributions between antenatal and intrapartum glycaemic control towards the development of neonatal hypoglycaemia.

4.3 Method

4.3.1 Ethics Approval

This study was approved by the Human Research Ethics Committee of the Western Sydney Local Health District HREC/13/WESTMEAD/16, SSA/13/WMEAD/48, SSA/13/NEPEAN/33.
4.3.2 Patient Selection

This is a retrospective study of all women with pre-gestational diabetes who attended antenatal clinic at Westmead, Blacktown or Nepean Hospital and subsequently delivered at these hospital within the period of December 2012 to April 2015.

Inclusion criteria were

- singleton pregnancy
- maternal age > 16
- use of insulin therapy during pregnancy.

Exclusion criteria included

- pregnancy loss
- delivery at gestational age < 32 weeks
- neonatal weight < 1.5kg at delivery
- incomplete data availability.

4.3.3 Antenatal Management and Peripartum Management

Antenatal management of pre-gestational diabetes incorporated reviews from a team consisting of obstetricians, endocrinologists, midwives, dietitians and diabetes educators. The glycaemic target during pregnancy was based on the ADIPS 1998 guidelines(18) aiming for a fasting blood glucose level (BGL) ≤ 5.5mmol/L and a 2hour post prandial BGL ≤ 7mmol/L.

All oral hypoglycaemic agents except Metformin were routinely ceased at the diagnosis of pregnancy or first attendance for those with pre-gestational type 2 diabetes. Cessation of Metformin occurred at the discretion of the individual treating endocrinologist. Insulin therapy was utilized in pregnancy in those with type 1 diabetes, pre-gestational insulin requiring type 2 diabetes, and pre-gestational non-insulin requiring type 2 diabetes unable to reach glycaemic target with lifestyle modification alone.

For intrapartum management, all women who had type 1 diabetes, or had type 2 diabetes but required more than 30 units of insulin per day were routinely placed on an insulin-dextrose infusion at the onset of labour with hourly glucometer BGL monitoring. Subcutaneous Insulin therapy was ceased during labour for women with type 2 diabetes who required less than 30 units of insulin per day with their BGL monitored via the glucometer on an hourly
basis. If their BGL exceeded 7mmol/L during labour, then an insulin-dextrose infusion would be commenced titrating for a BGL target of 4 – 7mmol/L.

4.3.4 Neonatal Hypoglycaemia Management

According to hospital protocol, all neonates of women on insulin therapy have peripheral glucometer BGL monitoring occurring within the 1st hour of delivery, then prior to feeding at 4 hourly intervals until 3 consecutive BGL reading are >2.5mmol/L. Neonates with birthweight <2.5kg or >4.5kg were given bottle feeding within the 1st hour of delivery. Neonates <1.5kg or <30 weeks gestation were commenced on IV dextrose from delivery. In this study, neonatal hypoglycaemia was defined as BGL≤2.5mmol/L as treatment for neonatal hypoglycaemia occurred at this level according to hospital protocol. Initial treatment involved bottle feeding of breastmilk or formula at 5mL/kg at 3hourly intervals. Should neonatal hypoglycaemia be significantly low, prolonged, or unresponsive to initial treatment, then the neonate would be managed in neonatal ICU (intensive care unit) with intravenous 10% dextrose.

4.3.5 Data Collection

The 3 year retrospective study was conducted on women who delivered at Westmead, Blacktown and Nepean Hospital from June 2012 to April 2015. Data collection was performed via access of the patient’s paper and electronic medical records held by the hospital as well as the Obstetrix database held by the Obstetrics Department of each hospital. Basic demographic data was collected on all participants including age, country of birth, BMI at delivery, parity, smoking status, past medical history, and antepartum medications. Maternal pregnancy data collected for analysis as potential predictors of neonatal hypoglycaemia included pre-gestational HbA1c, 3rd trimester HbA1c, maternal metformin use in pregnancy, peak total daily insulin dose, total daily insulin dose in last week of pregnancy, use of insulin-dextrose infusion for labour, duration of insulin-dextrose infusion during labour, average rate of insulin-dextrose infusion, peak, trough and average maternal BGL in the last 24hours of pregnancy (if ≥3 BGL readings available in the last 24hours of pregnancy), standard deviation of maternal BGL in the last 24hours of pregnancy (if ≥5 BGL readings available in the last 24hours of pregnancy), last maternal BGL prior to delivery
(within 1.5 hours of delivery). Neonatal data collected for analysis included neonatal birth centile (neonatal birth centile calculated via the Customised Centile Calculator GROW v6.7.5.2(209), adjusting for maternal age, parity, pre-pregnancy BMI via recall, country of birth, neonatal sex, gestation and weight), SGA (<10th birth centile), LGA (>90th birth centile), gestation of delivery, preterm birth (<37 weeks gestation).

Outcome measures included neonatal hypoglycaemia as a categorical variable defined by blood glucose level ≤2.5mmol/L requiring medical intervention, 1st neonatal recorded blood glucose level within 1.5 hours of birth, trough neonatal blood glucose level within the 1st 24 hours of delivery, timing of neonatal hypoglycaemia and timing of the trough neonatal BGL.

HbA1c levels were analysed via the Bio-Rad Variant II analyser HPLC assay (2012 – August 2014) or the Siemens Vista analyser immunoassay (August 2014 – April 2015). Recorded blood glucose levels included both capillary and plasma glucose levels. The capillary blood glucose levels were measured via either peripheral glucometer (Optium Xceed meter from 2012 - 2014, and the StatStrip Xpress glucometer from 2014-2015), or Haemaccue in neonates only. The plasma glucose levels were measured by the Ortho-Clinical Diagnostics Fusion 5.1 testing system (2012 – 2014) or the Siemens Dimension Vista 1500 Analyser (2014 – 2015).

4.3.6 Statistical Analysis

The last maternal BGL before delivery was converted into a categorical variable via clinically significant ranges for meaningful analysis, with BGL<4mmol/L representing maternal hypoglycaemia, 4 – 7mmol/L representing normoglycaemia, and >7mmol/L representing maternal hyperglycaemia in pregnancy. Similarly, the gestation of delivery was divided into clinically meaningful categories of <37 weeks representing prematurity, 37 – 38 weeks for mild prematurity, and ≥38 for full term delivery. Duration of insulin dextrose infusion was distributed into tertiles.

Comparison of normally distributed data was performed via the student t-test or ANOVA. Comparison of non-parametric data was performed via the Mann-Whitney U test or Kruskal-Wallis. Comparison of categorical data was performed via the Pearson’s Chi-Square test. Spearman’s correlation was used for correlation between 2 non-parametric continuous variables. Logistic regression was utilized for prediction testing of binary outcomes. Multiple
regression was utilized for multivariable analysis of continuous outcomes. Logarithmic transformation was utilized where appropriate for non-parametric data. P values <0.05 were considered significant.

### 4.4 Results

#### 4.4.1 Demographics

A total of 163 files were reviewed. There were 4 miscarriages/foetal death in utero, 3 extreme premature delivery <32 weeks gestation, and 13 subjects with inadequate documentation that were excluded from the analysis, leaving a total of 143 subjects analysed in this study. The demographic information on maternal age, maternal delivery BMI, parity, smoking status and type of pre-gestational diabetes are shown in Table 12. Apart from a higher proportion of smokers in the mother who had babies with neonatal hypoglycaemia (19.5% vs 3.6%, p=0.006), the other demographic statuses were fairly evenly distributed between the cohorts of women who had babies with and without neonatal hypoglycaemia. The proportion of neonatal hypoglycaemia was similar between mothers with type 1 and type 2 diabetes.

Table 12: Table of Maternal Demographics in Neonatal Hypoglycaemia Study

<table>
<thead>
<tr>
<th>Demographic Parameter</th>
<th>Neonatal hypoglycaemia N=87</th>
<th>No neonatal hypoglycaemia N=56</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal Age</td>
<td>32.13±5.61</td>
<td>31.41±5.95</td>
<td>0.47</td>
</tr>
<tr>
<td>Maternal delivery BMI^</td>
<td>36.97±7.35</td>
<td>34.67±8.03</td>
<td>0.12</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
<td>0.34</td>
</tr>
<tr>
<td>0</td>
<td>37.9% (33)</td>
<td>35.7% (20)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>48.3% (42)</td>
<td>57.1% (32)</td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td>13.8% (12)</td>
<td>7.1% (4)</td>
<td></td>
</tr>
<tr>
<td>Maternal Smoking</td>
<td>19.5% (17)</td>
<td>3.6% (2)</td>
<td>0.006</td>
</tr>
<tr>
<td>Type 1 Diabetes</td>
<td>29.9% (26)</td>
<td>30.4% (17)</td>
<td>0.95</td>
</tr>
<tr>
<td>Type 2 Diabetes</td>
<td>70.1% (61)</td>
<td>69.6% (39)</td>
<td></td>
</tr>
</tbody>
</table>

Percentages are based on column proportions.

^n=116
4.4.2 Predictors of neonatal hypoglycaemia

In our study, 60.8% (n=87) of the neonates developed hypoglycaemia. Of those with neonatal hypoglycaemia, 54% (n=47) required IV dextrose management. One neonate required IV glucagon. The results of the univariate analysis for neonatal hypoglycaemia are shown in Table 13. Based on our data, the higher the maternal 3rd trimester HbA1c, the higher the risk of neonatal hypoglycaemia, with every 1% increase in HbA1c raising the odds of developing neonatal hypoglycaemia by 66% (95% CI 14 – 141%, p=0.008). Neonatal hypoglycaemia also occurred more frequently in babies who were LGA (OR=3.74, 95% CI 1.67 – 8.35, p=0.001), or preterm (OR=2.68, 95% CI 1.19 – 6.02, p=0.02). No factors of intrapartum glycaemic control were associated with neonatal hypoglycaemia.

On multivariate analysis, significant independent predictors of neonatal hypoglycaemia were maternal smoking (OR=6.66, 95%CI 1.41-31.44, p=0.02), neonatal large for gestation (OR=3.71, 95%CI 1.61 – 8.56, p=0.002), and preterm birth (OR=2.61, 95%CI=1.10 – 6.15, p=0.03). However, this model was only able to explain 16% of the variability of neonatal hypoglycaemia in our study group.
Table 13: Predictors of neonatal hypoglycaemia

<table>
<thead>
<tr>
<th>Predictor</th>
<th>N</th>
<th>Neonatal hypoglycaemia</th>
<th>No neonatal hypoglycaemia</th>
<th>Odds Ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-gestational HbA1c (%)</td>
<td>130</td>
<td>7.65 (6.3 – 9.0)</td>
<td>7.20 (6.0 – 8.4)</td>
<td>0.233</td>
<td></td>
</tr>
<tr>
<td>3rd Trimester HbA1c (%)</td>
<td>127</td>
<td>6.3 (5.55 – 7.05)</td>
<td>6.0 (5.25 – 6.75)</td>
<td>1.66 (1.14 – 2.41)</td>
<td>0.008</td>
</tr>
<tr>
<td>Metformin use in pregnancy</td>
<td>143</td>
<td>18.4% (16)</td>
<td>16.1% (9)</td>
<td>0.72</td>
<td></td>
</tr>
<tr>
<td>Peak total daily insulin dose (units/day)</td>
<td>139</td>
<td>102 (64–141)</td>
<td>77 (36 – 119)</td>
<td>0.21</td>
<td></td>
</tr>
<tr>
<td>Total daily insulin dose in last week of pregnancy (units/day)</td>
<td>140</td>
<td>90 (53 – 127)</td>
<td>79 (40 – 118)</td>
<td>0.43</td>
<td></td>
</tr>
<tr>
<td>Use of insulin-dextrose infusion</td>
<td>143</td>
<td>53.6% (30)</td>
<td>60.9% (87)</td>
<td>0.39</td>
<td></td>
</tr>
<tr>
<td>Duration of insulin-dextrose infusion (hr)</td>
<td>83</td>
<td>6.0 (2.5 – 9.5)</td>
<td>7.0 (3.0 – 11.0)</td>
<td>0.70</td>
<td></td>
</tr>
<tr>
<td>Average rate of insulin-dextrose infusion (units/hr)</td>
<td>82</td>
<td>0.7 (0.45 – 0.95)</td>
<td>0.5 (0.15 – 0.85)</td>
<td>0.37</td>
<td></td>
</tr>
<tr>
<td>Peak maternal BGL (mmol/L)</td>
<td>108</td>
<td>8.6 (6.9 – 10.3)</td>
<td>7.9 (5.6 – 10.2)</td>
<td>0.40</td>
<td></td>
</tr>
<tr>
<td>Trough maternal BGL (mmol/L)</td>
<td>108</td>
<td>4.1 (3.3 – 5.0)</td>
<td>4.3 (3.7 – 5.0)</td>
<td>0.94</td>
<td></td>
</tr>
<tr>
<td>Average maternal BGL (mmol/L)</td>
<td>108</td>
<td>5.8 (4.9 – 6.7)</td>
<td>5.8 (5.1 – 6.6)</td>
<td>0.42</td>
<td></td>
</tr>
<tr>
<td>Last maternal BGL (mmol/L)</td>
<td>137</td>
<td>5.8 (4.7 – 6.9)</td>
<td>5.8 (4.8 – 6.8)</td>
<td>0.87</td>
<td></td>
</tr>
<tr>
<td>Standard deviation of maternal BGL (mmol/L)</td>
<td>92</td>
<td>1.4 (0.9 – 2.0)</td>
<td>1.3 (0.9 – 1.7)</td>
<td>0.48</td>
<td></td>
</tr>
<tr>
<td>LGA</td>
<td>143</td>
<td>44.8% (39)</td>
<td>17.9% (10)</td>
<td>3.74 (1.67 – 8.35)</td>
<td>0.001</td>
</tr>
<tr>
<td>Preterm</td>
<td>143</td>
<td>36.8% (32)</td>
<td>17.9% (10)</td>
<td>2.68 (1.19 – 6.02)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

All categorical variables expressed in column percentage (sample size).
All continuous variables expressed in median and interquartile range.
4.4.3 Predictors of 1st neonatal BGL

The median and interquartile range of the first neonatal BGL within the first 1.5 hr of delivery was 3.3 mmol/L (2.2 – 4.4) with a range of 0.3 mmol/L to 18.7 mmol/L. 35% (n=50) of the neonates in the study had their 1st BGL within the hypoglycaemic range. Of the neonates who had hypoglycaemia within the first 24 hours, 57% had hypoglycaemia upon their 1st BGL check.

The results of the univariate predictor analysis for the 1st neonatal BGL are shown in Table 14. There was a positive correlation (see Graph 1) between the 1st neonatal BGL with the last maternal BGL (correlation co-efficient 0.20, p=0.02). Further analysis was then performed with last maternal BGL as 3 clinically relevant categorical variables of BGL<4.0 representing maternal hypoglycaemia, BGL 4 – 7 representing within target maternal euglycaemia, and BGL>7.0 representing maternal hyperglycaemia. The median 1st neonatal BGL was higher in mothers whose last delivery BGL was hyperglycaemic compared to those controlled within the target range (4.2mmol/L vs 3.1mmol/L). Yet, mothers whose last BGL was within the hypoglycaemic range did not have a lower median neonatal 1st BGL compared to mothers within the euglycaemic range. There was a significant positive relationship between the gestation of delivery and the 1st neonatal BGL (Graph 2), with the median 1st neonatal BGL being 3.6mmol/L in those born ≥38 weeks gestation, 2.9mmol/L in those born 37-38 weeks of gestation, and 2.5mmol/L in those born <37 weeks gestation. Neonates born with LGA also have a significantly lower 1st BGL (3.6mmol/L vs 2.9mmol/L).

On multivariate analysis, the last maternal BGL, gestation of delivery and LGA were independent predictors of the 1st neonatal BGL. The 1st neonatal BGL was 54% (95% CI 20 – 98, p=0.001) higher in mothers whose last BGL was hyperglycaemic >7mmol/L compared to those within the target range of 4 – 7mmol/L. The 1st neonatal BGL was 25% lower in neonates born prior to 37 weeks gestation (95% CI 5 – 40, p=0.02) and 24% lower in neonates born between 37 – 38 weeks gestation (95% CI 0.3 – 42, p=0.05) when compared to neonates born at term ≥38 weeks gestation. The 1st neonatal BGL was 22% (95% CI 4 – 37, p=0.03) lower in those with LGA. This multivariate model explained for 17% of the variability in the 1st neonatal BGL.
Table 14: Predictors of 1st neonatal BGL

<table>
<thead>
<tr>
<th>Predictor</th>
<th>N</th>
<th>Correlation coefficient</th>
<th>Median 1st neonatal BGL</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-pregnancy HbA1c (%)</td>
<td>129</td>
<td>-0.062</td>
<td></td>
<td>0.49</td>
</tr>
<tr>
<td>3rd trimester HbA1c (%)</td>
<td>125</td>
<td>0.022</td>
<td></td>
<td>0.81</td>
</tr>
<tr>
<td>Peak daily insulin requirement (units/day)</td>
<td>137</td>
<td>-0.069</td>
<td></td>
<td>0.43</td>
</tr>
<tr>
<td>Total daily insulin in last week of pregnancy (units/day)</td>
<td>138</td>
<td>0.05</td>
<td></td>
<td>0.53</td>
</tr>
<tr>
<td>Average rate of insulin infusion (units/hr)</td>
<td>82</td>
<td>-0.08</td>
<td></td>
<td>0.50</td>
</tr>
<tr>
<td>Use of insulin-dextrose infusion</td>
<td></td>
<td></td>
<td></td>
<td>0.10</td>
</tr>
<tr>
<td><strong>Had Insulin-dextrose infusion</strong></td>
<td>83</td>
<td>3.6 (2.3 – 4.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>No insulin-dextrose infusion</strong></td>
<td>60</td>
<td>3.1 (2.2 – 3.90)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of insulin dextrose infusion (hr)</td>
<td>83</td>
<td>0.11</td>
<td></td>
<td>0.33</td>
</tr>
<tr>
<td>Peak BGL during last 24hrs of labour (mmol/L)</td>
<td>106</td>
<td>-0.01</td>
<td></td>
<td>0.91</td>
</tr>
<tr>
<td>Trough BGL during last 24hrs of labour (mmol/L)</td>
<td>106</td>
<td>0.04</td>
<td></td>
<td>0.69</td>
</tr>
<tr>
<td>Average BGL during last 24hrs of labour (mmol/L)</td>
<td>106</td>
<td>0.015</td>
<td></td>
<td>0.88</td>
</tr>
<tr>
<td>Last BGL before delivery (mmol/L)**</td>
<td></td>
<td></td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>&lt;4</td>
<td>14</td>
<td>3.6 (2.5 – 4.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-7</td>
<td>93</td>
<td>3.1 (2.1 – 4.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;7</td>
<td>28</td>
<td>4.2 (2.0 – 6.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Continuous variable</strong></td>
<td>135</td>
<td>0.20</td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>Standard deviation of maternal BGL in last 24hrs of labour (mmol/L)</td>
<td>91</td>
<td>-0.05</td>
<td></td>
<td>0.64</td>
</tr>
<tr>
<td>Gestation of Delivery (weeks)</td>
<td></td>
<td></td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>&lt;37</td>
<td>42</td>
<td>2.5 (1.4 – 3.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥37</td>
<td>74</td>
<td>3.6 (2.7 – 4.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Continuous variable</strong></td>
<td></td>
<td>0.21</td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>Smoking status*</td>
<td></td>
<td></td>
<td></td>
<td>0.20</td>
</tr>
<tr>
<td><strong>Smoking in pregnancy</strong></td>
<td>19</td>
<td>3.1 (2.4 – 3.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>No smoking in pregnancy</strong></td>
<td>122</td>
<td>3.4 (2.3 – 4.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neonatal birth centile*</td>
<td></td>
<td></td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td>LGA</td>
<td>47</td>
<td>2.9 (2.0 – 3.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No LGA</td>
<td>94</td>
<td>3.6 (2.5 – 4.7)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Mann-Witney U test
**Kruskal Wallis test
Graph 1: Scatter Graph of 1st Neonatal BGL vs Last Maternal BGL
Graph 2: Scatter Graph of gestation of delivery vs 1\textsuperscript{st} neonatal BGL
4.4.4 Predictors of trough neonatal BGL

In the neonates with hypoglycaemia, the median and interquartile range of the neonatal trough BGL was 1.85 (1.35 – 2.35) mmol/L with the minimum BGL being 0.3 mmol/L. In those without hypoglycaemia, the median neonatal trough BGL was 3.1 (2.65 - 3.55) mmol/L.

The results of the univariate predictor analysis for the trough neonatal BGL are shown in Table 15. A higher pre-pregnancy HbA1c, higher 3rd trimester HbA1c, higher rate of insulin infusion, higher peak maternal BGL in labour, higher mean maternal BGL in labour, earlier gestation of delivery and LGA were associated with a lower trough neonatal BGL. However on multivariate analysis, only LGA and gestation of delivery remained significant. The trough BGL of neonates with LGA were 0.52 (0.21 – 0.82) mmol/L lower than babies without LGA (p=0.001). Compared to neonates born ≥38 weeks gestation, the more premature the neonate, the lower the trough BGL, whereby those born 37 – 38 weeks gestation had a trough BGL that was 0.40 (0.01 – 0.80) mmol/L lower (p=0.05), whereas those born <37 weeks gestation had a trough BGL that was 0.56 (0.23 – 0.89) mmol/L lower (p=0.001). The multivariate model explained for 17% of the variability in trough neonatal BGL.
<table>
<thead>
<tr>
<th>Predictor</th>
<th>N</th>
<th>Correlation co-efficient</th>
<th>Median trough neonatal BGL (mmol/L)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-pregnancy HbA1c</td>
<td>125</td>
<td>-0.19</td>
<td></td>
<td>0.037</td>
</tr>
<tr>
<td>3rd trimester HbA1c</td>
<td>122</td>
<td>-0.25</td>
<td></td>
<td>0.005</td>
</tr>
<tr>
<td>Peak daily insulin requirement</td>
<td>134</td>
<td>-0.12</td>
<td></td>
<td>0.15</td>
</tr>
<tr>
<td>Total daily insulin in last week of pregnancy</td>
<td>135</td>
<td>-0.06</td>
<td></td>
<td>0.50</td>
</tr>
<tr>
<td>Average rate of insulin infusion</td>
<td>81</td>
<td>-0.22</td>
<td></td>
<td>0.05</td>
</tr>
<tr>
<td>Use of insulin-dextrose infusion</td>
<td></td>
<td></td>
<td></td>
<td>0.90</td>
</tr>
<tr>
<td><em>Had Insulin-dextrose infusion</em></td>
<td>82</td>
<td></td>
<td>2.2 (1.6 – 2.8)</td>
<td></td>
</tr>
<tr>
<td><em>No insulin-dextrose infusion</em></td>
<td>55</td>
<td></td>
<td>2.2 (1.5 – 2.9)</td>
<td></td>
</tr>
<tr>
<td>Duration of insulin dextrose infusion (hr)</td>
<td>82</td>
<td>0.001</td>
<td></td>
<td>0.99</td>
</tr>
<tr>
<td>Peak BGL in labour</td>
<td>103</td>
<td>-0.20</td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>Trough BGL in labour</td>
<td>103</td>
<td>-0.08</td>
<td></td>
<td>0.42</td>
</tr>
<tr>
<td>Mean BGL in labour</td>
<td>103</td>
<td>-0.21</td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td>Last BGL prior to delivery</td>
<td>132</td>
<td>-0.11</td>
<td></td>
<td>0.19</td>
</tr>
<tr>
<td>SD of maternal last 24hrs BGL</td>
<td>88</td>
<td>-0.14</td>
<td></td>
<td>0.19</td>
</tr>
<tr>
<td>Smoking status*</td>
<td></td>
<td></td>
<td></td>
<td>0.26</td>
</tr>
<tr>
<td>*Smoking in pregnancy</td>
<td>19</td>
<td>2.1 (1.7 – 2.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>*No smoking in pregnancy</td>
<td>118</td>
<td>2.3 (1.6 – 2.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neonatal birth centile*</td>
<td></td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>LGA</em></td>
<td>47</td>
<td>1.9 (1.3 – 2.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>No LGA</em></td>
<td>90</td>
<td>2.5 (1.9 – 3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestation of delivery**</td>
<td></td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤37</td>
<td>42</td>
<td>1.8 (1.1 – 2.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>37.1 – 38</td>
<td>25</td>
<td>2.1 (1.5 – 2.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥38 (n=57)</td>
<td>70</td>
<td>2.5 (2.1 – 3.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Mann-Witney U test

**Kruskal-Wallis
4.5 Discussion

4.5.1 Antenatal Factors Influence the Risk of Neonatal Hypoglycaemia

In this study, we did not find that intrapartum glycaemic control such as the peak, average, trough, standard deviation of maternal BGL or the use of insulin dextrose infusion affected the outcome of neonatal hypoglycaemia. Instead, the factors associated with neonatal hypoglycaemia were long term antepartum factors such as maternal smoking, neonatal LGA, 3rd trimester HbA1c and preterm delivery. The significance of 3rd trimester maternal HbA1c was lost in multivariate analysis and this may be due to possible collinearity with LGA given that poor glycaemic control in pregnancy lead to LGA. LGA is commonly reported as a risk factor for neonatal hypoglycaemia. It has been suggested that foetal growth in-utero is mediated by the growth effect of the foetus’ endogenous insulin in response to the level of passive diffusion of glucose from the maternal placenta. (149) Thus the presence of LGA may be a better clinical predictor of the neonates with hyperinsulinism induced by maternal hyperglycaemia than maternal HbA1c. Our finding of preterm birth as a risk factor for neonatal hypoglycaemia is also consistent with the existing literature. The pathophysiology for this phenomenon include the immaturity of enzymes for gluconeogenesis and the lack of fat stores associated with prematurity. (138, 143)

Our study had a novel finding of maternal smoking in pregnancy as an independent risk factor of neonatal hypoglycaemia. The limited literature has not shown a direct influence of maternal smoking on neonatal hypoglycaemia,(140) but it is known that smoking increases the risk of intrauterine growth retardation, small for gestation and premature delivery which may lead to neonatal hypoglycaemia(210). However when these factors were adjusted in our multivariate model, smoking remained an independent predictor. Demonstration of smoking as a modifiable predictor of neonatal hypoglycaemia in addition to the evidence of increased risks of adverse maternal and foetal outcomes of pregnancy induced hypertension, placenta rupture, premature birth, congenital defects, offspring obesity, stillbirth, further strengthens the importance of smoking cessation in pregnancy (211).
4.5.2 Antepartum and Intrapartum Factors Influence the 1st Neonatal BGL

The last maternal BGL was shown to have a positive correlation with the 1st neonatal BGL. The passive diffusion of maternal glucose across the placenta likely explains this positive association in the hyperglycaemic spectrum, and is supported by previous study demonstrating the high positive correlation between cord glucose and last maternal glucose (147, 149, 181). However, there appears to be a threshold effect whereby the 1st neonatal BGL was not lower if the last maternal BGL was in the hypoglycaemic range of <4mmol/L. This could be explained by the fact that the neonate is capable of glycogenolysis hence not reliant on maternal glucose in the intrapartum period.

Despite the positive association between last maternal BGL and 1st neonatal BGL, there was no association between last maternal BGL and neonatal hypoglycaemia. Thus the influence of the last maternal BGL appears to be transient, and a higher last maternal BGL was not protective of the development of neonatal hypoglycaemia. As 43% of the neonates developed hypoglycaemia after their 1st BGL, the 1st neonatal BGL is a poor indicator of the neonate’s risk of developing hypoglycaemia. An elevated 1st neonatal BGL should not be interpreted as a reassuring sign because it may be the remnant of the maternal BGL contribution prior to delivery.

4.5.3 Antepartum and Intrapartum Factors Influence the Trough Neonatal BGL

A mixture of intrapartum and antenatal factors appeared to be correlated with the trough neonatal BGL. Two studies (187, 188) had previously shown that higher mean and peak intrapartum maternal BGL were associated with increased risk of neonatal hypoglycaemia. However in our study, despite the negative relationship between the mean and peak maternal intrapartum BGL with the trough neonatal BGL, we did not find that these factors were associated with increased risk of neonatal hypoglycaemia as a binary outcome. Based on the management protocol of the study institutions, intrapartum BGL were aimed between 4 – 7mmol/L. The median peak maternal intrapartum BGL in our study was 8.3 (6.4 – 10.3) mmol/L with 68% of the women having a peak BGL>7mmol/L. Hence our study may not have sufficient women with highly elevated BGL to contribute towards lowering of the trough neonatal BGL into the hypoglycaemic range. It was also found that a higher rate of
insulin-dextrose infusion was associated with lower trough neonatal BGL whereas the use of insulin-dextrose infusion as a binary variable did not influence the trough neonatal BGL or the development of neonatal hypoglycaemia. Hence, rather than the direct effect of the exogenous insulin, the higher rate of insulin-dextrose infusion may be an indicator of more severe maternal insulin resistance and thus identifying women with more difficulty achieving euglycaemia in pregnancy in both the intrapartum and antenatal period.

The finding of higher pre-pregnancy HbA1c and 3rd trimester HbA1c with lower trough neonatal BGL may be explained by the foetal hyperinsulinaemia effect in response to poor maternal glycaemic control. LGA and preterm delivery were consistently and independently associated with all three outcomes examined in our study. This suggests that LGA may be a strong indicator of the end effect of maternal hyperglycaemia or the degree of foetal hyperinsulinaemia. This relationship between early antepartum maternal hyperglycaemia and adverse hyperinsulinaemic neonatal outcome is concordant with hypothesis of fetal glucose steal phenomenon (212). Early maternal hyperglycaemia may have primed the development of fetal hyperinsulinaemia, which in turn generated a greater gradient for the glucose flux across the placenta manifesting on the fetal side as hyperinsulinaemic fetopathy but at the maternal side as a deceptive euglycaemia in late pregnancy. This adds evidence for clinicians to counsel women with pre-existing diabetes not only on optimizing glycaemic control during pregnancy but also during pre-pregnancy planning. Whilst preterm labour may also be a result of suboptimal glycaemic control, it can also cause neonatal hypoglycaemia via alternative mechanisms of foetal organ immaturity. The prominence of these antepartum risk factors within the multivariate analysis for both neonatal hypoglycaemia and trough neonatal BGL suggests that antepartum glycaemic control may have a stronger influence on neonatal glycaemia than intrapartum glycaemic control.

4.5.4 Limitations and Strengths of the Study

The high incidence of neonatal hypoglycaemia in our study of 60.8% is consistent with other studies of similar population of women with pre-gestational diabetes. Yet, despite the aspects of antepartum and intrapartum glycaemic control examined, our model only explained 16% of the variability in the occurrence of neonatal hypoglycaemia. Given the incidence of neonatal hypoglycaemia in non-diabetic pregnant pregnancy at term with normal gestation size is only ~10%, it appears that our knowledge on the cause of this increased risk in
diabetic pregnancy is still very limited, and perhaps a reflection of the many constraints of performing such a study. As an observational study, any associations found can only be used as hypothesis generating rather than causal. The accuracy of this study is limited by the use of BGL readings taken from a combination of peripheral glucometer and formal plasma glucose levels. The maternal and neonatal BGL readings were not undertaken systematically in all subjects. In addition, there may be neonates managed with intravenous dextrose for other birth complications such as poor feeding or respiratory distress that may confound the BGL readings despite best efforts to identify them through medical record documentations. As aforementioned, due to the mothers’ glycaemic control already being managed in the antepartum and intrapartum period, our study was only able to observe the effect of a relatively narrow range of maternal glycaemia on the neonatal BGL, hence may be limited in the power to detect statistically significant effects. Therefore interpretation of the results needs to take this into consideration. The strength of his study include the comprehensive range of intrapartum and antepartum glycaemia factors investigated, as well as the use of multivariate regression analysis to investigate for independent risk factors.

4.6 Study Conclusion

Neonatal BGL in the first 24 hours of birth is associated with both antepartum and intrapartum maternal glycaemic control. Antepartum factors of 3rd trimester HbA1c, LGA, maternal smoking, along with pre-term delivery exert influence on the risk of developing neonatal hypoglycaemia. In particular, LGA and preterm delivery, in addition to the novel factor of smoking, were found to be independent risk factors for neonatal hypoglycaemia. Higher maternal mean and peak intrapartum BGL, and higher rate of insulin-dextrose infusion are associated with lower neonatal trough BGL. However when maternal glycaemia is managed within the range of 4 – 7mmol/L, intrapartum glycaemic control do not contribute to increased risk of neonatal hypoglycaemia. Pre-pregnancy HbA1c may have a role on neonatal BGL on delivery.
5. Thesis Conclusion

This thesis aimed to address issues relating to current controversies in the management of diabetes in pregnancy. We conducted 2 studies in the gestational diabetes and the pre-gestational diabetes populations. The findings of these studies increase the body of evidence which may assist with resolving the controversies and development of evidence based recommendations in clinical management to improve pregnancy outcome.

In women with gestational diabetes, controversy exists for the implementation of the new IADPSG2010 diagnostic criteria given that it was derived from one observational study with a lack of clinical randomized control trial showing benefits of treatment of GDM diagnosed with these criteria. We conducted a retrospective cohort study to examine the appropriateness and potential consequences of a change in criteria. This enabled us to compare the pregnancy outcomes of women who were treated under the ADIPS1998 GDM diagnostic criteria with untreated women who would be newly diagnosed via the IADPSG2010 GDM criteria and those without GDM, as well as examine the effect of obesity. Our study had demonstrated that within our multiethnic population, women who would newly be classified as GDM under the IADPSG 2010 diagnostic criteria were indeed at increased risk of adverse pregnancy outcomes. Treatment of GDM in those who satisfied the ADIPS 1998 diagnostic criteria was able to lower the risk of certain adverse pregnancy outcomes to a similar level as those without GDM, but the finding that there was increased SGA in the ADIPS1998 Only group is of concern. On the basis of these observational data, it would be reasonable to argue for the adoption of the new criteria. However, there remains a lack of data on the pregnancy outcomes of women treated via the new IADPSG2010 criteria and whether this new group of women identified will yield better pregnancy outcomes without the risk of SGA under treatment. The interpretation of our data is limited as women in this study generally only received a 75 g GTT if they failed the 50 g GCT, and the results may be different if all women went straight to a 3 point GTT, as this would include women who have a normal 50g GCT, or hyperglycaemia exclusively at the 1hour time point of the 75g OGTT, who are presumably at a lower risk than the GDM women in our study cohort. Given that many institutions have commenced universal 3 point OGTT in pregnancy, data will soon become available for a more comprehensive analysis of the risk imposed by the IADPSG2010-only cohort as well as treatment outcomes to better evaluate the validity of changing the diagnostic
criteria for GDM. Yet ultimately, it remains important to conduct further high grade studies, in particular a RCT of treatment of GDM under the new IADPSG2010 diagnostic criteria, to fully resolve these controversies.

This study also demonstrated that for women who did not have GDM under the ADIPS 1998 criteria, there is a stronger association between adverse pregnancy outcomes and obesity, than with GDM diagnosed by the 2010 IADPSG criteria only. Yet there are minimal resources and guidelines available to address this equally, if not more, concerning risk factor. There is evidence from the Cochrane review(123) that in overweight and obese women, combined diet and exercise counselling results in reduction in maternal hypertension, 15% decreased risk of infant macrosomia and lower maternal gestational weight gain. In addition, weight loss up to 4kg in obese women has been reported to be associated with improved pregnancy outcomes in pre-eclampsia, LGA, caesarean section, with minimal risk of SGA (213). Despite these existing evidence on the efficacy of treatment in optimizing pregnancy outcome, there is a relative lack of emphasis on the management of obesity in pregnancy.

Given the finite resources available, efficiency in utilisation of resources is important, and where possible, interventions should be based on evidence of improved outcomes. There is evidence for improved pregnancy outcomes when treating women with a fasting glucose level of $\geq 5.3$ mmol/L (74) and those with a 2 hour glucose $\geq 7.8$ mmol/L (73). These cut-offs are slightly lower than, but are similar to the ADIPS1998 criteria. The aforementioned Cochrane review provides some evidence to treat mothers with obesity. On the other hand, this study has shown that treatment of women in the old ADIPS1998 Only group may not be entirely appropriate, given the increased rate of SGA with treatment of this group. Whilst the new IADPSG-only group is indeed at higher risk of adverse outcomes, treatment data is not available, and thus there is little evidence to support treatment on the basis of this diagnostic criterion.

With the above facts in mind, it may be appropriate to focus resource efforts and the highest intensity of treatment on the groups with the highest risk or for whom there is strong evidence of the benefit of treatment, without causing harm. These would be women with both GDM-both (fasting BGL$\geq 5.5$mmol/L and/or 2hour post-prandial BGL$\geq 8.5$mmol/L) and obesity, followed by women with either GDM-both or obesity. The IADPSG-only cohort could be included when treatment data is available. This tiered (Figure 4) approach allows for concentration of resource towards patients at highest risk and with the greatest impact of
treatment. We cannot afford to dilute the limited resources in areas where there is little evidence of treatment benefit.

Figure 4: Stratification of Adverse Pregnancy Outcome Risks Factors (GDM status and BMI)

In women with pre-gestational diabetes, we examined the controversy of the impact of maternal glycaemic control on the risk of neonatal hypoglycaemia. In particularly we explored the respective roles of antepartum and intrapartum maternal glycaemic control. Table 16 summarises the predictors of neonatal BGL based on this study. We provided evidence to show that both antepartum and intrapartum maternal glycaemic control has influences on the neonatal BGL in the 1st 24hours of delivery. However when intrapartum maternal glycaemia is kept between 4 – 7mmol/L, there is no association with increased risk of neonatal hypoglycaemia.
Based on the findings of this study, some recommendations regarding pregnancy management aimed at reducing the risk of neonatal hypoglycaemia in women with pre-gestational diabetes can be made. Risk reduction of neonatal hypoglycaemia starts at pregnancy planning. We recommend women with pre-gestational diabetes seek review with their health professional prior to pregnancy to ensure optimization of glycaemic control is achieved prior to attempting pregnancy. In addition, continued optimization of glycaemic control in the antenatal period is important, especially during the 3rd trimester where the frequency of review may need to be intensified to ensure normoglycaemia in a period which is usually associated with rapid increase in insulin requirement (214). The optimization of general obstetric care is also of importance to minimize the risk of pre-term delivery. Interval growth scans, especially in the 3rd trimester can be utilized in delivery planning, such that findings of LGA can alert the obstetric and paediatric team regarding the increased risk of neonatal hypoglycaemia. During the intrapartum period, the study findings reinforce the current institutional practice of aiming for tight glycaemic control, defined as a glucose level between 4 – 7 mmol/L, and this may be well be best achieved via an insulin-dextrose infusion. Post-delivery, at least two neonatal BGLs are required at 1 hour intervals to confirm absence of neonatal hypoglycaemia given the 1st neonatal BGL is a reflection of the last maternal BGL rather than the ability of the neonate to maintain normoglycaemia.

The management of diabetes in pregnancy is complex. The studies in this thesis have provided some new evidence to support, add to, or counter current guidelines. It is through the constant renewal and accumulation of studies can we obtain enough reliability on the

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**Table 16: Summary of Predictors of Neonatal BGL**

<table>
<thead>
<tr>
<th>Predictors of neonatal hypoglycaemia</th>
<th>Predictors of first neonatal BGL</th>
<th>Predictors of trough neonatal BGL</th>
</tr>
</thead>
<tbody>
<tr>
<td>LGA</td>
<td>Last maternal BGL before delivery</td>
<td>Pre-gestational HbA1c</td>
</tr>
<tr>
<td>Preterm delivery</td>
<td>Gestation of delivery</td>
<td>3rd trimester HbA1c</td>
</tr>
<tr>
<td></td>
<td>LGA</td>
<td>Average rate of insulin infusion in labour</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Peak maternal BGL in labour</td>
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<tr>
<td></td>
<td></td>
<td>Mean maternal BGL in labour</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LGA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gestation of delivery</td>
</tr>
</tbody>
</table>

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consistency of study outcomes to resolve controversies. In turn each resolution leads to an addition to the evolution of evidence based management guidelines to further improve pregnancy outcomes in women affected by diabetes.
6. References


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