Is Stratification of "Low-Risk"
Women with Gestational Diabetes Mellitus to Usual Antenatal Care Safe?

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DECLARATION

This thesis is a presentation of my original research work. Wherever contributions of others are involved, every effort is applied to indicate this clearly, with due reference to the literature, and acknowledgement of people who offered help. This work has not been submitted previously for the award of any other degree or diploma at any university or other tertiary institution. Part of the results has been published as an abstract in American Diabetes Association’ 74th Scientific Sessions.

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Abstract

Introduction: Gestational Diabetes Mellitus (GDM) patients are stratified into low-risk and high-risk groups in Canberra, Australia, according to whether their glycaemic control reaches the target levels with lifestyle measures only. High-risk patients, in whom glycaemic control is unsatisfactory, are referred to a multidisciplinary “diabetes in pregnancy” team, while low-risk patients continue regular antenatal care. The aims of this study were to test the accuracy of the current stratification system of GDM treatment in Canberra, and to access whether low-risk patients have satisfactory perinatal outcomes compared to the high-risk patients, considering their less intensive antenatal care.

Methods: A retrospective clinical audit of GDM patients treated between 01/01/2010 and 30/06/2014 was conducted. Maternal demographic data and neonatal/maternal clinical outcomes data were analysed including, for key outcomes, comparison with outcomes for the background population in the ACT.

Results: Low-risk (n=509) compared to high-risk (n=466) GDM mothers were younger (31.7±4.8 vs 32.6±5.3 years-old, p=0.009), leaner [body mass index (BMI) 26.3±6.7 vs 29.3±7.5 kg/m², p<0.001], and less parous (0.73±1.0 vs 0.98±1.2 times, p<0.001), with less past GDM (13.2% vs 23.2%, p<0.001), less family history of diabetes (55.4% vs 67.0%, p=0.001), and a lower fasting glucose level in the oral glucose tolerance test (OGTT) (4.9±0.5 mmol/l vs 5.0±0.8 mmol/l, p<0.001). There were more South-East
Asian women in the low-risk group (19.4% vs 11.9%, p=0.002). Low-risk mothers had lower rates of pregnancy-induced hypertension (PIH) (6.1% vs 11.8%, p=0.002; ACT 5.7%), induced labour (23.2% vs 50.6%, p<0.001) and elective Caesarean-section (CS) (14.1% vs 20.4%, p=0.010). Rates of emergency CS were similar in the low- and high-risk groups (16.7% vs 19.1%, p=0.328; ACT 14.9%). The rate of preterm delivery (delivery before 37 weeks gestation) was higher in the low-risk group, (9.8% vs 6.0%, p=0.014; ACT 8.3%), attributed to a higher rate of spontaneous preterm delivery (6.1% vs 2.6%, p=0.010). After adjusting for maternal age, BMI, parity, smoking status and alcohol consumption during pregnancy, premature delivery was still more likely in the low-risk group (odds ratio 1.897, 95% Confidence Interval 1.137-3.164).

For neonatal outcomes, there were no differences in rates of babies with birth weight >4000g (5.5% vs 7.1%, p=0.309; ACT 11.8%), shoulder dystocia (1.6% vs 1.5%, p=0.930), hypoglycaemia (6.1% vs 7.1%, p=0.532), respiratory disorder (6.3% vs 6.0%, p=0.857), and hyperbilirubinaemia (8.8% vs 10.7%, p=0.320). There was a trend towards a lower rate of customized large for gestational age infants (cLGA) in the low-risk group, compared to the high-risk group (6.1% vs. 9.4%, p= 0.050). The rate of neonatal admission to the intensive care unit (NICU)/special care nursery (SCN) was higher in the low-risk group (16.7% vs 10.9%, p=0.010; ACT 14.7%). However, this difference might have been attributed to the different NICU/SCN admission criteria adopted by the two evaluated hospitals.

**Conclusion:** The stratification system is efficient: low-risk compared to high risk patients were younger, leaner, and had less past GDM, less family history of diabetes.
and lower fasting glucose during the OGTT. Adverse pregnancy outcomes were either less (PIH, delivery interventions, cLGA) or similar (emergency CS and some neonatal complications) in the low compared to high risk group. One exception was a higher rate of preterm delivery among low-risk women. Some adverse neonatal outcomes for low-risk women were also higher than in the general ACT population. The treatment pathway of low-risk GDM patients has considerable merit, but requires further assessment and optimisation to ensure safety.
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>ABE</td>
<td>Acute bilirubin encephalopathy</td>
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<tr>
<td>ACHOIS</td>
<td>Australian Carbohydrate Intolerance Study in Pregnant Women</td>
</tr>
<tr>
<td>ACOG</td>
<td>American Congress of Obstetricians and Gynaecologists</td>
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<td>ACT</td>
<td>Australian Capital Territory</td>
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<tr>
<td>ACTH-DIPS</td>
<td>ACT Health Diabetes in Pregnancy Service</td>
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<tr>
<td>ACTPAS</td>
<td>ACT patients’ administration System</td>
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<td>ADA</td>
<td>American Diabetes Association</td>
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<td>ADIPS</td>
<td>Australasian diabetes in pregnancy society</td>
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<td>AGA</td>
<td>Appropriate for gestational age</td>
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<td>BGL</td>
<td>Blood glucose level</td>
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<td>BOS</td>
<td>Birthing Outcomes System</td>
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<td>CHO</td>
<td>Carbohydrate</td>
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<td>CIS</td>
<td>ACT Pathology Clinical Integration System</td>
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<td>CIS</td>
<td>Clinical Information System</td>
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<td>CPAP</td>
<td>Continuous positive airway pressure</td>
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<td>CRIS</td>
<td>Clinical Record Information System</td>
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<td>CRP</td>
<td>C-reactive protein</td>
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<td>Abbreviation</td>
<td>Definition</td>
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<tr>
<td>CS</td>
<td>Caesarean section</td>
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<td>CTG</td>
<td>Cardiotocography</td>
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<tr>
<td>DIPS-MDC</td>
<td>Multidisciplinary Diabetes in pregnancy Clinic</td>
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<tr>
<td>D-LGA</td>
<td>Disproportionate LGA babies</td>
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<tr>
<td>ECFC</td>
<td>Endothelial colony-forming cell</td>
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<td>EMH</td>
<td>Early onset neonatal hypocalcaemia</td>
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<td>FHR</td>
<td>Fetal heart rate</td>
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<tr>
<td>GAD65As</td>
<td>Glutamic acid decarboxylase</td>
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<td>GCT</td>
<td>Glucose challenge test</td>
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<tr>
<td>GDM</td>
<td>Gestational diabetes mellitus</td>
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<td>GH</td>
<td>Gestational hypertension</td>
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<td>GI</td>
<td>Glycaemic Index</td>
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<td>GLUT4</td>
<td>Glucose transporter type 4</td>
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<tr>
<td>GPs</td>
<td>General practitioners</td>
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<tr>
<td>HAPO</td>
<td>Hyperglycaemia and Adverse Pregnancy Outcomes</td>
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<td>HBGI</td>
<td>High Blood Glucose Index</td>
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<tr>
<td>hct</td>
<td>Haematocrit</td>
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<tr>
<td>HIE</td>
<td>Hypoxic ischemic encephalopathy</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>HLA-G</td>
<td>Human leukocyte antigen-G</td>
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<tr>
<td>IA-2As/IA-2Bs</td>
<td>Insulinoma-associated antigens</td>
</tr>
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<td>IAAs</td>
<td>Insulin autoantibodies</td>
</tr>
<tr>
<td>IADPSG</td>
<td>International Association of the Diabetes and Pregnancy Study Groups</td>
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<tr>
<td>ICAs</td>
<td>Islet cell autoantibodies</td>
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<tr>
<td>IL-1</td>
<td>Interleukin 1</td>
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<tr>
<td>IL-6</td>
<td>Interleukin 6</td>
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<tr>
<td>IRS-1</td>
<td>Insulin receptor substrate 1</td>
</tr>
<tr>
<td>IUGR</td>
<td>Intrauterine growth restriction</td>
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<tr>
<td>LADA</td>
<td>Latent autoimmune diabetes of adulthood</td>
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<tr>
<td>LGA</td>
<td>Large for gestational age</td>
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<tr>
<td>LNH</td>
<td>Late onset neonatal hypocalcaemia</td>
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<tr>
<td>MAS</td>
<td>Meconium aspiration syndrome</td>
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<tr>
<td>MiG</td>
<td>Metformin in Gestational Diabetes</td>
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<td>MNT</td>
<td>Medical nutrition therapy</td>
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<tr>
<td>MODY</td>
<td>Maturity-onset diabetes of the young</td>
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<tr>
<td>MOH</td>
<td>Ministry of Health of the People's Republic of China</td>
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<tr>
<td>Acronym</td>
<td>Description</td>
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<tr>
<td>MRNs</td>
<td>Medical Record Numbers</td>
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<tr>
<td>NDDG</td>
<td>National Diabetes Data Group</td>
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<tr>
<td>NF-kB</td>
<td>Nuclear factor kappa-light-chain-enhancer of activated B cells</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute for Health and Care Excellence</td>
</tr>
<tr>
<td>NICU</td>
<td>Neonatal intensive care unit</td>
</tr>
<tr>
<td>NIH</td>
<td>National Institutes of Health</td>
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<tr>
<td>NPH</td>
<td>Neutral Protamine Hagedorn</td>
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<tr>
<td>NST</td>
<td>Fetal Non-stress Test</td>
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<tr>
<td>OCT</td>
<td>Contraction stress test</td>
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<tr>
<td>OGTT</td>
<td>Oral glucose tolerance test</td>
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<tr>
<td>OPG</td>
<td>Osteoprotegerin</td>
</tr>
<tr>
<td>OVD</td>
<td>Operative vaginal delivery</td>
</tr>
<tr>
<td>PCOS</td>
<td>Polycystic ovary syndrome</td>
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<tr>
<td>PE</td>
<td>Preeclampsia</td>
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<tr>
<td>PI</td>
<td>Phosphatidylinositol</td>
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<tr>
<td>PI</td>
<td>Ponderal index</td>
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<tr>
<td>PIH</td>
<td>Pregnancy-induced hypertension</td>
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<td>P-LGA</td>
<td>Proportionate LGA babies</td>
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<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>PPAR</td>
<td>Peroxisome proliferator-activated receptor</td>
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<tr>
<td>PROM</td>
<td>Prelabour rupture of membranes</td>
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<tr>
<td>PTH</td>
<td>Parathyroid hormone</td>
</tr>
<tr>
<td>RANZCOG</td>
<td>The Royal Australian and New Zealand College of Obstetricians and Gynaecologists</td>
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<tr>
<td>RCT</td>
<td>Randomised controlled trials</td>
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<tr>
<td>RD</td>
<td>Respiratory distress</td>
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<tr>
<td>RDS</td>
<td>Respiratory distress syndrome</td>
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<tr>
<td>Sca</td>
<td>Serum calcium</td>
</tr>
<tr>
<td>SCN</td>
<td>Special Care Nurseries</td>
</tr>
<tr>
<td>SGA</td>
<td>Small for gestational age</td>
</tr>
<tr>
<td>sPTD</td>
<td>Spontaneous preterm birth</td>
</tr>
<tr>
<td>TOFU</td>
<td>Offspring Follow-Up</td>
</tr>
<tr>
<td>TTN</td>
<td>Transient tachypnoea of the newborn</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
Table of Contents

CHAPTER ONE LITERATURE REVIEW OF GESTATIONAL DIABETES MELLITUS (GDM) AND RESEARCH HYPOTHESIS .................................................. 18

1.1 History of GDM ........................................................................................................... 18

1.2 GDM pathology ........................................................................................................... 20
  1.2.1. Auto-immune GDM .......................................................................................... 20
  1.2.2. Monogenetic diabetes ...................................................................................... 21
  1.2.3 Other pathological pathways ............................................................................. 22

1.3 Diagnostic criteria of GDM ......................................................................................... 24
  1.3.1 Historic diagnostic criteria of GDM ................................................................. 24
  1.3.2 Hyperglycaemia and Adverse Pregnancy Outcomes (HAPO) study, and new diagnostic criteria for GDM ................................................................. 25
  1.3.3 Diagnostic criteria for GDM in Australia ......................................................... 32

1.4 Short term complications of GDM .............................................................................. 33
  1.4.1 Neonatal short term complications .................................................................. 34
  1.4.2 Maternal short term complications ................................................................. 55

1.5 Long term complications of GDM ............................................................................. 68
  1.5.1 Neonatal long term complications .................................................................... 69
1.5.2 Maternal long term complications ........................................ 73

1.6 GDM treatment ........................................................................ 77
  1.6.1 Rationale for treatment ..................................................... 77
  1.6.2 Self-glucose monitoring .................................................... 78
  1.6.3 Target blood glucose levels .............................................. 80
  1.6.4 Medical nutrition therapy (MNT) ...................................... 81
  1.6.5 Exercise (physical activity) ................................................. 85
  1.6.6 Insulin treatment .............................................................. 87
  1.6.7 Oral hypoglycaemic agents .............................................. 90
  1.6.8 Obstetric issues regarding GDM treatment .................... 93

1.7 Rationale for this research ....................................................... 95
  1.7.1 High-risk group patients may have worse perinatal outcomes 96
  1.7.2 Low-risk group patients may not necessarily have better outcomes ................................................................. 98

1.8 Research hypothesis and aims ................................................ 101
  1.8.1 Research hypothesis ....................................................... 101
  1.8.2 Research aims ............................................................... 101

CHAPTER TWO RESEARCH SETTING AND METHODOLOGY ............... 103

2.1 General information about the Australian Capital Territory (ACT) area ........................................................................ 103
2.2 Pregnancy related health care in Canberra .......................... 104

2.3 Diagnosis of GDM in the ACT ........................................... 104

2.4 Stratified care system for GDM in the ACT .......................... 106
  2.4.1 GDM education session (part one) ............................... 106
  2.4.2 GDM education session (part two) ............................... 107
  2.4.3 Patient review and stratification into low and high-risk pathways 108

2.5 Methodology ........................................................................ 115
  2.5.1 Ethics approval .............................................................. 115
  2.5.2 Subjects ........................................................................ 115
  2.5.3 Data Collection .............................................................. 117
  2.5.4 Data management .......................................................... 128
  2.5.5 Statistical methods ......................................................... 131

CHAPTER THREE RESULTS ...................................................... 133

3.1 General information ............................................................. 133

3.2 Maternal demographic information ...................................... 135
  3.2.1 Maternal age, BMI, gestational age at first appointment, gestational age at GDM diagnosis, number of gestations and parity .............................. 135
  3.2.2 History of GDM, family history of diabetes ....................... 138
  3.2.3 Smoking status and alcohol consumption ....................... 140
  3.2.4 Maternal ethnicity ......................................................... 142
3.2.5 Maternal pre-existing complications.................................144
3.2.6 GCT and OGTT results......................................................145
3.2.7 Summary of maternal information.....................................147

3.3 Maternal outcomes..................................................................148
  3.3.1 Gestational hypertension (GH) and preeclampsia (PE)........148
  3.3.2 Gestational age, preterm birth and post-term birth..............149
  3.3.3 Onset of birth, mode of delivery and methods of birth........151
  3.3.4 Reasons for elective CS and emergency CS......................154
  3.3.5 Perineal status and suture................................................158
  3.3.6 Delivery complications....................................................161
  3.3.7 Hospitalization and after delivery bleeding......................162
  3.3.8 Summary of maternal outcomes......................................163

3.4 Neonatal Outcomes .............................................................166
  3.4.1 Birth status......................................................................166
  3.4.2 Apgar Score......................................................................167
  3.4.3 Birth weight......................................................................169
  3.4.4 Neonatal complications....................................................173
  3.4.5 Summary of the neonatal outcomes.................................178

3.5 NICU admission information in The Canberra Hospital............180
  3.5.1 General Information........................................................180
  3.5.2 Neonatal Complications....................................................181
  3.5.3 Summary of NICU admission information..........................189
3.6 Subgroup analysis of high-risk group patients who continued diet treatment (HRD) .......................................................... 191

3.6.1 Maternal demographic information ........................................... 191
3.6.2 Results of HbA1c, TSH and Vitamin D ........................................... 197
3.6.3 Maternal outcomes of the three groups ....................................... 199
3.6.4 Neonatal outcomes of the three groups ...................................... 202
3.6.5 Summary of subgroup analysis of HRD group .............................. 205

CHAPTER FOUR DISCUSSION ......................................................... 207

4.1 DISCUSSION FOR AIM ONE .................................................. 208
4.1.1 Baseline demographic information .............................................. 209
4.1.2 Maternal pre-existing conditions ................................................. 213
4.1.3 Conclusion for aim one ............................................................. 216

4.2 Discussion for aim two: ............................................................. 217
4.2.1 Maternal outcomes ................................................................. 218
4.2.2 Neonatal outcomes ................................................................. 225
4.2.4 Analysis of patients in the high-risk group who continued diet treatment alone (HRD) .............................................................. 234
4.2.5 Conclusion for aim two ............................................................ 237

4.3 Advantages and limitations ........................................................ 238
4.3.1 Advantages ............................................................................ 238
4.3.2 Limitations and future studies ............................................................ 239

4.3.3 Suggestions for the improvement of the current treatment system
................................................................................................................................. 240

4.4 Final Conclusion: ...................................................................................... 241

APPENDIX ....................................................................................................... 243

Appendix 1 Ethical approval letter from The Canberra Hospital .............. 244

Appendix 2 Ethical approval letter from the Calvary Hospital ................. 246

Appendix 3 Indicators for Initiating Phototherapy ................................. 248

Appendix 4 The number of patients who presented as percentage in the
results (part one) ............................................................................................... 249

Appendix 5 The number of patients who presented as percentage in the
results (part two) ............................................................................................... 256

Appendix 6 List of flowchart, tables and charts ........................................ 258

REFERENCE .................................................................................................. 262
CHAPTER ONE LITERATURE REVIEW OF GESTATIONAL DIABETES MELLITUS (GDM) AND RESEARCH HYPOTHESIS

1.1 History of GDM

Reports of Diabetes Mellitus, a disease originally described as “too great emptying of urine”, were initially found in Egyptian manuscripts dated 1500 B.C. (1). Aretaeus the Cappadocian coined the word ‘diabetes’ after the Greek word for siphon, and described it as a condition in which “fluids do not remain in the body, but use the body only as a channel through which they may flow out”, in the first century A.D (2). In 1769, William Cullen, a British clinician, added the adjective mellitus (Latin, ‘sweet like honey’) to distinguish this variant of diabetes from others such as diabetes insipidus in which the urine was tasteless (3). The modern understanding of diabetes mellitus is that it is a group of metabolic diseases characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action, or both (4).

For more than a hundred years, doctors observed that women who developed diabetes before pregnancy were more likely to have severe adverse effects on fetal and neonatal outcomes (5). In 1824, Bennewitz first described diabetes in pregnancy in Germany; in his case, the patient presented intensive thirst, recurrent glycosuria and had a baby that weighed almost 5.5 kg (6).

However, during 1940-1950, it was recognized that patients who developed diabetes years after pregnancy also suffered from higher rates of fetal and neonatal mortality (7). The term gestational diabetes mellitus (GDM), coined by Elsie Reed in 1957
(8), became accepted at that time and was defined as the development of abnormalities in carbohydrate metabolism in pregnancy (9-11). Dr O’Sullivan pioneered the diagnosis of gestational diabetes by establishing a statistical upper limit for glycaemic normality in pregnancy, through 100-g oral glucose tolerance testing (OGTT) in the 1960s (12). In 1979, the National Diabetes Data Group (NDDG) defined GDM as “glucose intolerance that has its onset or recognition during pregnancy, regardless of the severity of the disease or whether the condition persists after pregnancy.” “Women with diabetes who become pregnant are not included (13). This definition was endorsed by the International Workshop – Conference on Gestational Diabetes and became popularly used all over the world (14-17). However, there are currently concerns that this popularly used definition includes too wide a range of glucose abnormalities, especially for those with undetected pre-gestational diabetes.

To address this issue, the International Association of Diabetes and Pregnancy Study Groups (IADPSG) proposed a new definition of GDM, which is “the condition associated with degrees of maternal hyperglycaemia less severe than those found in overt diabetes but associated with an increased risk of adverse pregnancy outcomes”, and divided patients who had hyperglycaemia first detected during pregnancy into two subgroups, that is, overt diabetes and GDM (18). This new definition was endorsed in the new World Health Organisation (WHO) and Endocrine Society guidelines (19, 20), but was refused by the Australasian Diabetes in Pregnancy society (ADIPS). In the latest ADIPS guidelines, authors insisted that a definitive diagnosis of non-gestational diabetes cannot be made until the postpartum period (21).
1.2 GDM pathology

Pregnancy is characterized as a diabetogenic condition. To meet the energy demands of the fetus and to prepare for delivery and lactation, the maternal metabolism changes from carbohydrates to lipids (22). Insulin resistance, which starts from the second trimester and goes on throughout the whole pregnancy, may contribute to this change. The increased placental secretion of hormones, such as progesterone, cortisol, placental lactogen, prolactin, and growth hormone, combined with increased maternal adiposity, are responsible for the raised insulin resistance. To counteract the decrease of insulin sensitivity, insulin secretion increases consistently from the first trimester and peaks at the third trimester (23-25). It has been shown that insulin secretion increases by 200 – 250%, to balance a 50% decrease in insulin-moderated glucose disposal during pregnancy, to maintain normal glucose levels (26).

Gestational diabetes mellitus happens when impaired β-cell cannot produce enough insulin to compensate for the increased insulin resistance of pregnant patients. There are different pathways leading to GDM, including autoimmune and monogenetic abnormalities in β-cell functions and most commonly, the same pathway as type 2 diabetes.

1.2.1. Auto-immune GDM:

Auto-immune GDM accounts for a small population of GDM patients (less than 10%), and is correlated with the risk of type 1 diabetes in different ethnicities (27). Islet antibodies include autoantibodies to islet cell cytoplasm (islet cell autoantibodies [ICAs]), to native insulin (insulin autoantibodies [IAAs]), to glutamic acid decarboxylase
(GAD65As) and to tyrosine phosphatases (insulinoma-associated antigens [IA-2As and IA-2Bs]) (28). The frequency of GAD65A and IA2 positivity is higher than other autoantibodies in GDM patients but the antibody titres are lower compared to the type 1 diabetes patients (28).

GDM patients with autoantibodies are younger, leaner, have lower prevalence of diabetes in first-degree relatives, have lower fasting plasma insulin and experience lower weight gain during pregnancy, but need insulin treatment more frequently compared to the autoantibody negative GDM patients (29). Auto-immune GDM patients have higher risk of developing type 1 diabetes in the future (30) and share some similar characteristics with latent autoimmune diabetes of adulthood (LADA) patients (31).

1.2.2. Monogenetic diabetes:

Monogenetic diabetes is caused by autosomal dominant mutations, with an early onset but a mild and relatively uncomplicated course (32). Previous monogenic diabetes was termed “maturity-onset diabetes of the young (MODY)”, but currently, the term “monogenetic diabetes” is found to be more suitable (33). The more common mutations include: mutations in the glucokinase gene (MODY2), which presents as mild fasting hyperglycaemia(34) and its prevalence ranges from 0% to 12% among all GDM patients (35-37); mutations in the transcription factor HNF-1α (MODY3), which causes slow progressive deterioration of insulin secretion (34), and accounts for up to 1% of GDM (38, 39); mutations in the transcription factor HNF-4α (MODY 1), which may cause
macrosomia and neonatal hypoglycaemia (34), and has a rate of 1% in GDM patients (40). There are other rare mutations, for example, mutations in the PDX1 gene (38) and mutations in the mitochondrial genome that combine with neurosensory hearing loss (41).

1.2.3 Other pathological pathways

However, most GDM cases share the similar pathological pathway as type 2 diabetes, due to β-cell secretion deficiency on the background of chronic insulin resistance (42).

The cellular mechanisms for chronic insulin resistance are well described in the literature. In skeletal muscle, decreased levels of phosphatidylinositol (PI) 3-kinase activity is caused by increasing expression of the p85α subunit of PI 3-kinase, the negative competitor to forming a PI 3-kinase heterodimer with the p110 subunit (43, 44). In addition, lower levels of insulin receptor substrate 1 (IRS-1) tyrosine phosphorylation and decreased concentrations of IRS-1 protein (45, 46) contribute to the reduced translocation of glucose transporter type 4 (GLUT4) to the plasma membrane, and result in decreased insulin-stimulated glucose uptake (47). In adipose tissue, insulin resistance is induced by reduction of the transcription factor peroxisome proliferator-activated receptor (PPAR)-γ1 gene and protein (48). The exact cause of chronic insulin resistance is still unknown. Potential culprits could be obesity, inflammation in adipose tissue, plasma and placenta, and hyperlipidaemia with increased levels of leptin, tumour necrosis factor-alpha (TNF-α), interleukin 6(IL-6), interleukin 1 (IL-1), C-reactive protein
(CRP), and decreased levels of adiponectin (49-52).

Not all patients who have insulin resistance develop hyperglycaemia, due to compensation via increased insulin secretion. Therefore, β-cell dysfunction plays a critical role in the pathology of GDM. Insulin response to oral and intravenous glucose are lower in GDM patients compared to normal pregnant women, even after adjustments for insulin resistance (53). A mismatch between β-cell function and mass (54), as well as failure of the cell to respond adequately to secretagogue stimulation, could be a possible mechanisms of β-cell dysfunction (55). Genetic defects may predispose patients to β-cell dysfunction.

Multiple genes interact with environment factors, which can lead to GDM. Environmental factors include increased excessive energy intake and decreased physical activity (56). Genes related to the development of GDM are mostly associated with the regulation of insulin secretion, and include TCF7L2, GCK, KCNJ11, CDKAL1, IGF2BP2, MTNR1B, Gly972Arg, and IRS1 (57).

Other than the well-recognized causes of GDM in the above discussion, other hypotheses have also been suggested. For example, the development of GDM could be triggered by an antigenic load that is the fetus itself, which is analogous to the development of type 2 diabetes in some patients submitted to organ transplantation. Human leukocyte antigen-G (HLA-G) expression that responds to the load of fetal antigens and the complex interactions between this response and the increased nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) activity that cause increased insulin resistance might also explain the development of GDM (58).
1.3 Diagnostic criteria of GDM

1.3.1 Historic diagnostic criteria of GDM

The diagnosis of GDM is a very complicated issue that has been intensely debated for almost 40 years but still has not achieved worldwide consensus. The first diagnostic criteria were made available in 1964. These criteria were based on identifying women at high-risk for development of diabetes after pregnancy (59). GDM was diagnosed by using a 100g OGTT test (12), and this method is still used today with some modifications. NDDG started to test plasma or serum instead of whole venous blood. This test method also changed from Somogyi-Nelson technology to the new approach using glucose oxidase and hexokinase, which is more specific to glucose (60). Another common diagnostic strategy, which has almost the same cut-off values of diabetes mellitus outside pregnancy, was used by the World Health Organization (WHO). The WHO diagnostic criteria were initially defined in 1980 as a fasting plasma glucose level $\geq 8 \text{ mmol/l}$ or/and a 2-h glucose level (after 75g of glucose load) $\geq 11 \text{ mmol/l}$ in the OGTT. However, after lowering the threshold in 1985 and 1999, the criteria changed to a fasting glucose of $\geq 6.1 \text{ mmol/l}$ or/and a 2-h OGTT glucose of $\geq 7.8 \text{ mmol/l}$, which are widely used in developing countries. The WHO criteria were based on the increased risk for diabetic patients of developing microvascular complications, especially retinopathy, in the future (61).
1.3.2 Hyperglycaemia and Adverse Pregnancy Outcomes (HAPO) study, and new diagnostic criteria for GDM

None of the previous diagnostic criteria for GDM were based on the prevalence of perinatal adverse outcomes. The Hyperglycaemia and Adverse Pregnancy Outcomes (HAPO) is considered a landmark research in this area, and included 23,316 patients from different ethnic backgrounds. It showed that higher maternal glucose levels during an OGTT are associated with an increased risk of complications for both mothers and babies. The HAPO study found a strong and continuous association between maternal glucose concentrations, even in mild hyperglycaemic levels, with adverse birth outcomes, including birth weight > 90th percentile, primary caesarean section, clinical neonatal hypoglycaemia, cord-blood serum C peptide > 90th percentile, premature delivery, shoulder dystocia, intensive neonatal care admission, neonatal hyperbilirubinaemia, and maternal preeclampsia (62) (Chart 1).
Chart 1 – Maternal glucose concentration associated with adverse perinatal outcomes.

Fasting: category 1 = <4.2 mmol/l (75 mg/dl), 2 = 4.3-4.4 mmol/l (75-79 mg/dl), 3 = 4.5-4.7 mmol/l (80-84 mg/dl), 4 = 4.8-4.9 mmol/l (85-89 mg/dl), 5 = 5.0-5.2 mmol/l (90-94 mg/dl), 6 = 5.3-5.5 mmol/l (95-99 mg/dl), 7 = ≥5.6 mmol/l (100 mg/dl).

One-hour oral glucose tolerance test (OGTT): category 1 = ≤5.8 mmol/l (105 mg/dl), 2 = 5.9-7.3 mmol/l (106-132 mg/dl), 3 = 7.4-8.6 mmol/l (133-155 mg/dl), 4 = 8.7-9.5 mmol/l (156-171 mg/dl), 5 = 9.6-10.7 mmol/l (172-193 mg/dl), 6 = 10.8-11.7 mmol/l (194-211 mg/dl), 7 = ≥11.8 mmol/l (212 mg/dl).

Two-hour OGTT: category 1 = ≤5.0 mmol/l (90 mg/dl), 2 = 5.1-6.0 mmol/l (91-108 mg/dl), 3 = 6.1-6.9 mmol/l (109-125 mg/dl), 4 = 7.0-7.7 mmol/l (126-139 mg/dl), 5 = 7.8-8.7 mmol/l (140-157 mg/dl), 6 = 8.8-9.8 mmol/l (158-177 mg/dl), 7 = ≥9.9 mmol/l (178 mg/dl).

Based on the results of the HAPO study, the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) recommended new criteria for GDM diagnosis, with compared to the previous ADIPS diagnostic criteria, a one-step 75-g OGTT with a more stringent fasting cut-off value, the addition of a 1h cut-off value, and a less stringent 2h cut-off value at 24–28 weeks of gestation in women not previously diagnosed with overt diabetes. Moreover, only one abnormal value is sufficient for the GDM diagnosis. There are two main issues addressed by the new criteria. Firstly, IADPSG advised to screen for hyperglycaemia at the first prenatal clinic visit, in order to detect overt diabetes as soon as possible. Secondly, the cut-off value for the diagnostic OGTT test was based on reflecting a 75% (odds ratio 1.75) increased risk in three primary adverse outcomes of GDM, including birth weight >90th percentile, baby’s C-peptide >90th percentile and baby fat>90th percentile (63) (Flowchart 1).
Flowchart 1 – IADPSG diagnostic procedures of GDM.

There is hot debate on whether to implement these new criteria. The advantages of the new criteria are quite obvious. Firstly, the IADPSG guideline is the only one among all other guidelines in that it is based on pregnancy outcomes, and its diagnostic thresholds are specifically selected by using the pathophysiologic condition of hyperglycaemia in pregnancy (64). Secondly, it finally brings uniformity to GDM diagnosis and makes the comparisons of outcomes between different studies possible. Thirdly, the new guideline, as a one-step procedure, may be easier to implement by...
health care providers. Finally, the data in the HAPO trial was collected from more than 23,000 patients with different ethnicities, age, and BMI. Having adjusted for these potential confounders, the new guidelines are most likely to be suitable for the worldwide GDM population (65).

There are also many concerns regarding the IADPSG recommendations. There is a lack of evidence that patients diagnosed via the new GDM criteria would receive significant clinical benefit, in both maternal and neonatal outcomes (66). Compared to the ADA guidelines, using the IADPSG criteria will increase the number of GDM patients by 3 times in the United Arab Emirates, which will increase the strain on health systems (67). Similarly, the rate of GDM increased from 7.89% to 19.9%, almost twofold after using the IADPSG diagnostic criteria instead of the ADA criteria in the Chinese population (68). In Canada, there was also an increase in rates of GDM, from 7.9% to 9.4%, when using the IADPSG criteria (69). There is a limited number of studies focusing on the cost-effectiveness of the new screening consensus, and some have reported contradictory results (70, 71). Some organizations, for example the WHO (72), Ministry of Health of the People’s Republic of China (MOH) (73), and the Endocrine Society have decided to follow the IADPSG recommendations while other institutions, such as the American College of Obstetricians and Gynaecologists (ACOG) and the National Institutes of Health (NIH), have refused to accept the new criteria (74, 75). Interestingly, the American Diabetes Association (ADA) initially endorsed the IADPSG criteria in 2011, but in their latest published guidelines (2014), it stated that there is no uniform approach for GDM
diagnosis, and both the one-step strategy (IADPSG criteria) and two-step strategy (ACOG criteria) could be used (76, 77) (Table 1).

Table 1 –Recommendations for screening procedures and diagnostic criteria for GDM.

<table>
<thead>
<tr>
<th>Organization</th>
<th>Screen population</th>
<th>Type of test</th>
<th>Glucose load</th>
<th>Cut-off points</th>
<th>Number of criteria required</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO 1999</td>
<td>Not mentioned</td>
<td>One-step</td>
<td>75g</td>
<td>Fasting ≥ 6.1 mmol/l, 2h ≥ 7.8 mmol/l</td>
<td>≥1</td>
</tr>
<tr>
<td>WHO 2013</td>
<td>Not mentioned</td>
<td>One-step</td>
<td>75g</td>
<td>Fasting 5.1-6.9 mmol/l, 1h ≥ 10.0 mmol/l, 2h 8.5-11.0 mmol/l</td>
<td>≥1</td>
</tr>
<tr>
<td>ACOG 2013</td>
<td>Universal</td>
<td>Two-step</td>
<td>50g GCT 100g OGTT</td>
<td>GCT ≥ 7.8 mmol/l or 7.5 mmol/l* fasting ≥ 5.3 mmol/l, 1h ≥ 10.0 mmol/l, 2h ≥ 8.6 mmol/l, 3h ≥ 7.6 mmol/l</td>
<td>≥ 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Procedure</td>
<td>Criteria</td>
<td>Requirement</td>
<td></td>
</tr>
<tr>
<td>----------------</td>
<td>--------------</td>
<td>--------------------------</td>
<td>-------------------------------------------------------------------------</td>
<td>-------------</td>
<td></td>
</tr>
<tr>
<td>ADA 2014</td>
<td>Universal</td>
<td>Two- or one-step</td>
<td>50g GCT 100g OGTT Or 75g OGTT GCT ≥ 7.8 mmol/l or 7.2 mmol/l* 100g OGTT fasting ≥ 5.3 mmol/l 1h ≥ 10.0 mmol/l 2h ≥ 8.6 mmol/l 3h ≥ 7.8 mmol/l 75g OGTT Fasting ≥ 5.1 mmol/l 1h ≥ 10.0 mmol/l 2h ≥ 8.5 mmol/l</td>
<td>≥ 2</td>
<td></td>
</tr>
<tr>
<td>Endocrine</td>
<td>Universal</td>
<td>One-step</td>
<td>75g Fasting ≥ 5.1 mmol/l 1h ≥ 10.0 mmol/l 2h ≥ 8.5 mmol/l</td>
<td>≥ 1</td>
<td></td>
</tr>
<tr>
<td>Society 2013</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NICE 2015</td>
<td>Selective</td>
<td>One-step</td>
<td>75g Fasting ≥ 5.6 mmol/l 2h ≥ 7.8 mmol/l</td>
<td>≥ 1</td>
<td></td>
</tr>
</tbody>
</table>

WHO, World Health Organization; ACOG, American College of Obstetrician and Gynaecologists; ADA, American Diabetes Association; NICE, National Institute for Health and Care Excellence; GCT, Glucose challenge test;
OGTT, Oral glucose tolerance test; * ACOG recommended a lower cut-off point of GCT in high ethnic minorities with higher prevalence of GDM.

1.3.3 Diagnostic criteria for GDM in Australia

In Australia, the first diagnostic criteria were developed in 1991 (78). They are used nationwide with some modifications, even today. If a patient was suspected to be at high risk for GDM, an OGTT test could be performed at any stage of pregnancy. If the OGTT results were normal in early pregnancy, these patients would take another diagnostic OGTT test between 26 to 30 weeks of gestational age. Besides high-risk patients, all pregnant women were given a non-fasting glucose challenge test (GCT) between 26 to 28 weeks of gestational age. If the results of the GCT were positive (50g glucose load 1h > 7.8mmol/l or 75g glucose load 1h > 8.0mmol/l), patients would have a diagnostic 75g OGTT test before 30 weeks of gestational age. Patients would be diagnosed with GDM if their fasting glucose level was higher than or equal to 5.5 mmol/l or/and 2 hour glucose level higher than or equal to 8.0 mmol/l (79).

The Australasian Diabetes in Pregnancy Society (ADIPS) recently endorsed the IADPSG’s cut-off points for the diagnostic OGTT test. Additionally, the new guidelines recommended a 75g OGTT at first opportunity after conception in high-risk patients to detect undiagnosed overt diabetes (80). The research in this thesis included patients who were diagnosed with GDM from 2010 to 2014 when the previous ADIPS screening guidelines were still used (Table 2).
Table 2 –Screening and diagnosis of GDM in this research.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Timing for testing</th>
<th>Population</th>
<th>Glucose load</th>
<th>Cut-off points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical suspicion of GDM</td>
<td>Any stage</td>
<td>Selective</td>
<td>75g</td>
<td>Fasting ≥ 5.5 mmol/l or 2h ≥ 8.0 mmol/l</td>
</tr>
<tr>
<td>Screening (GCT)</td>
<td>26-28 weeks</td>
<td>Universal</td>
<td>50g</td>
<td>1h ≥ 7.8 mmol/l (50g)</td>
</tr>
<tr>
<td>Confirmative test (OGTT)</td>
<td>26-30 weeks</td>
<td>Women who had positive GCT results</td>
<td>75g</td>
<td>Fasting ≥ 5.5 mmol/l</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>75g</td>
<td>2h ≥ 8.0 mmol/l</td>
</tr>
</tbody>
</table>

GCT, Glucose challenge test; OGTT, Oral glucose tolerance test

1.4 Short term complications of GDM

It is known that pre-existing diabetes is associated with an array of maternal and neonatal adverse outcomes including gestational hypertension, preterm delivery, stillbirth, malformation, macrosomia, neonatal hypoglycaemia, neonatal hyperbilirubinaemia, neonatal respiratory distress, neonatal polycythaemia, neonatal hypocalcaemia and neonatal cardiomyopathy during pregnancy (81, 82). GDM is defined as any degree of glucose intolerance with onset of first recognition during pregnancy, including a wide spectrum of diseases, from undetected type 1 and type 2 diabetes to
mild glucose intolerance that disappears after birth. GDM patients might suffer from the same adverse perinatal outcomes as patients with pre-existing diabetes, but the incidence and the severity of these complications are significantly lower among GDM patients.

As previously described, the researchers of the HAPO study demonstrated that maternal glucose intolerance less severe than overt diabetes was associated with increased risk of neonatal birth weight above 90\textsuperscript{th} percentile and cord-blood serum C-peptide level above the 90\textsuperscript{th} percentile, primary caesarean delivery (CS), clinical neonatal hypoglycaemia, premature delivery, shoulder dystocia or birth injury, hyperbilirubinaemia, preeclampsia and neonatal intensive care unit (NICU) admission (83).

These adverse perinatal complications of GDM can be divided into short term neonatal complications, short-term maternal complications, long-term neonatal complications, and long term maternal complications.

1.4.1 Neonatal short term complications

1.4.1.1 Stillbirth and malformation

1) Stillbirth

The HAPO study did not find any association between the risk of stillbirth and maternal glucose intolerance less severe than overt diabetes (83). Fadl and collaborators also demonstrated similar results in a large cohort study that included 1,260,297
patients (10,525 had GDM) and aimed to analyse the maternal and neonatal outcomes among GDM patients. They found there was no difference in terms of the risk of stillbirth between GDM patients and non-GDM women (Adjusted OR 0.85, 95% CI 0.59-1.23, p=0.284) (84). However, the presence of fasting hyperglycaemia (>5.8 mmol/l) might have been associated with increased risk of stillbirth during the last 4-8 weeks of gestation, which might have been attributed to undetected overt diabetes among GDM patients (85).

2) Malformation

Pre-existing diabetes increases the risk of neonatal malformations due to poor maternal glycaemic control in the periconceptual period. Janssen and colleagues conducted a population based retrospective study involving 1511 patients with pre-existing diabetes and 8869 patients with GDM to examine the relationship between diabetes in pregnancy and the development of congenital malformations in the United States. The authors indicated that there was a slightly higher prevalence of malformation among babies of GDM mothers (OR 1.3, 95%CI 1.0-1.6), however the risk was significantly higher among infants of mothers with overt diabetes (OR 4.0, 95% CI 3.1-5.1) (86). Fadl and colleagues in Sweden also found a mild increase in the risk of neonatal malformation among GDM patients compared to non-GDM sufferers (Adjusted OR 1.19, 95% CI 1.02-1.39) (84).

Researchers demonstrated that there was an increased risk of a particular type of malformation among babies of GDM mothers, as well as babies of patients with pre-existing diabetes; these malformations include cardiac malformation, oesophageal
atresia and spinal anomalies (87). Interestingly, when analysing the relationship between major malformation and maternal blood glucose concentration at entry into prenatal care, the authors found that the rate of major malformation was 2.1% when the initial fasting plasma glucose (FPG) was < 6.6 mmol/l; 5.9% when FPG was between 6.6-11.0 mmol/l, and 12.9% when FPG exceeded 11 mmol/l (p< 0.0001) (88). Based on the available information, researchers concluded in a large literature review that the risk of malformation was slightly higher in pregnancies of women with GDM compared to the general population. However, this increased risk was probably associated with the presence of undiagnosed pre-existing diabetes among women with GDM (89).

1.4.1.2 Fetal overgrowth

Macrosomia, a common term for fetal overgrowth, is defined as birth weight higher than 4000g (National Institute for Health and Care Excellence) or 4500g (American College of Obstetrician and Gynaecologists). Larger for gestational age (LGA) is another term to describe fetal overgrowth, which corresponds to a birth weight ≥ 90th percentile for gestational age. This criterion can also identify excessive fetal growth in premature infants. Recently, more advanced percentile calculations have been made available for populations in specific countries, to enable adjustments for maternal height, maternal weight, parity, maternal ethnicity, gestational age and gender, and to provide more precise results for LGA (the customized LGA) rate (90, 91). The reasons for macrosomia could be divided into two categories: non-modifiable factors and modifiable factors. Non-modifiable factors include genes, epigenetic regulation, maternal age,
maternal height and fetal gender, while modifiable determinants include pre-gestational maternal BMI, gestational weight gain, maternal nutritional status, level of physical activity, smoking and metabolic parameters (92).

GDM has been known to be associated with an increased risk of fetal overgrowth for some time. According to the Pedersen Hypothesis, fetal hyperglycaemia caused by maternal hyperglycaemia, could induce hypertrophy of fetal β islet tissue and cause hyper-secretion of insulin. This extra insulin acts as a growth hormone and contributes to fetal overgrowth (93). In the HAPO study, the researchers demonstrated a strong continuous relationship between maternal hyperglycaemia, even below diagnostic glucose level of GDM, with increased rate of birth weight > 90th percentile and neonatal cord-blood serum C peptide > 90th percentile. This result supports the Pedersen hypothesis (62). Recently, maternal dyslipidaemia, another common metabolic disorder found in GDM, is suspected to be related to fetal overgrowth as well (94).

Fetal overgrowth has both short-term and long-term consequences. The babies’ short-term complications include birth trauma (shoulder dystocia, plexus injuries, and bone fractures), metabolic disorders (hypoglycaemia, hyperbilirubinaemia), fetal hypoxia and NICU admission (95-97). For those mothers who gave birth to overgrown babies, the adverse outcomes include prolonged labour, operative deliveries, perineal lacerations, uterine atonia, abnormal haemorrhage and a necessity for caesarean section deliveries (98, 99). Long-term complications for overgrown babies include increased susceptibility to diabetes, overweight, metabolic syndrome, asthma, persistent plexus injuries and cancer (especially breast cancer and childhood leukaemia)
Interestingly, infants of diabetic mothers are more likely to have disproportionate overgrowth that refers to excessive weight characterized by a high weight/length ratio. Anthropometric and skinfold measurements in newborns of mothers with gestational diabetes suggested a disproportionate pattern of growth in fetuses of diabetic mothers with increased tendency for deposition of subcutaneous fat (102). Compared to non-diabetic mothers, macrosomic babies born to diabetic mothers have a significantly higher rate of shoulder dystocia and Caesarean deliveries (103, 104). Previous studies also showed that disproportionate macrosomic babies have a higher rate of neonatal hypoglycaemia, hyperbilirubinaemia and acidosis compared to proportionate macrosomic babies and babies without macrosomia (105).

### 1.4.1.3 Shoulder Dystocia

Shoulder dystocia is objectively defined as “a prolonged head to body delivery time [i.e., more than 60 seconds], and/or the necessitated use of ancillary obstetric manoeuvres.” (106), and can be further categorized as mild and severe, according to the kind of manoeuvre applied (107). It results from a size discrepancy between the fetal shoulders and the pelvic outlet. The classic maternal risk factors include obesity, diabetes, excessive weight gain, high parity and a prior birth complicated by shoulder dystocia (108-110). Labour risk factors include prolonged first or second stages of labour and instrumental delivery (111-113). Vacuum extractions increase the risk of shoulder dystocia more than forceps deliveries (114). The risk of shoulder dystocia also increases
along with the increment of birth weight: risk is 5.2% for infants between 4000 to 4250g, 9.1% for those between 4250 to 4500g, 14.3% for those between 4500 to 4750g and 21.1% for those between 4750 to 5000g (115). Mansor and collaborators demonstrated a similar positive relationship between infants’ birth weight and the rate of shoulder dystocia (116).

Landon and associates found that the shoulder dystocia rate was higher among women with mild gestational diabetes compared to women with a normal GCT (approximately 4% vs. less than 1%) (117). Large observational studies also indicated that the incidence of shoulder dystocia appeared to be doubled across all birth weight categories, for babies born to diabetic mothers, both with overt diabetes and GDM. These rates are 12.2% for infants 4000-4250g, 16.7% for those 4250-4500g, 27.3% for those 4500-4750g, and 34.8% for those 4750-5000g, whereas the incidence rate of shoulder dystocia for non-diabetic mothers is 5.2% for infants 4000-4250g, 9.1% for those 4250-4500g, 14.3% for those 4500 to 4750, and 21.1% for those 4750-5000g (115). This increased rate could be attributed to the higher rate of disproportionate overgrowth among babies of GDM patients. Macrosomic infants born to diabetic mothers have large shoulders and extremity circumferences, decreased head-to-shoulder ratio, higher body fat and thicker upper-extremity skin folds compared with babies born to non-diabetic mothers (118). Furthermore, among GDM patients, maternal fasting hyperglycaemia was associated with increased risk of shoulder dystocia, with 1 mmol/l increases in fasting OGTT results leading to a two-fold increase in the rate of shoulder dystocia (Relative Risk 2.09, 95% CI 1.03-4.25) (119).
Shoulder dystocia increases morbidity and mortality in both mothers and babies. Common maternal complications are postpartum haemorrhage and unintentional extension of the episiotomy or laceration into the rectum (fourth-degree laceration) (120). Other complications include vaginal lacerations, cervical tears, bladder atony, and uterine rupture (121). For babies, the most common complication is temporary or prominent brachial plexus injuries, including Erbs palsy (C5, C6), Klumpke palsy (C8, T1), total brachial plexus palsy (C5-T1) and Horner’s syndrome (C5-T1 and facial nerve) (122, 123). Other rare complications include bone fracture (commonly clavicle or humerus), and hypoxic-ischemic encephalopathy and even death (123, 124). It is still controversial whether GDM patients who had shoulder dystocia will have worse outcomes compared to the glucose tolerant women who also suffered from shoulder dystocia (125, 126).

The manoeuvres for shoulder dystocia alleviation include McRoberts’ manoeuvre, suprapubic pressure, fetal rotational manoeuvres or posterior arm extraction (Woods’ corkscrew manoeuvre and Rubin’s manoeuvre), and “all-four” techniques. There are also other more aggressive techniques, for examples, the Zavanelli manoeuvre, symphysiotomy, hysterotomy and deliberate clavicular fracture (127, 128).

1.4.1.4 Neonatal hypoglycaemia

Neonatal hypoglycaemia was first described by Hartmann and Jaudon in 1937 (129) and has been associated with prominent brain damage for more than 40 years
The “numerical” definition of neonatal hypoglycaemia, meaning the blood glucose concentration cut-off point below which would create risk of long-term neurological and developmental consequences, has been continually debated all over the world (131). The most widely accepted cut-off value of hypoglycaemia is a glucose level less than 2.6 mmol/l, and it was based on an observational research done by Lucas et al in 1988 (132). Other published definitions range from a blood glucose concentration of less than 1.1 mmol/l in preterm birth and less than 1.7 mmol/l in term infants, to a plasma concentration of less than 2.5 mmol/l (133). The reasons why it is so difficult to achieve a uniform definition, are that healthy newborn infants also experience low glucose levels during the early postnatal period, and that newborn infants have the ability to compensate by producing other metabolic fuels and provide energy to maintain brain function, for example ketone bodies and lactate. There is also a lack of evidence regarding the correlation between the level of glucose concentration, and adverse neurologic and developmental outcomes (134).

Recently, the American Academy of Paediatrics stated that a specific concentration of glucose that can discriminate euglycaemia from hypoglycaemia, or predict acute or chronic irreversible neurologic damage could not be supported due to the lack of sufficient evidence (135). Instead, Hawdon proposed a new diagnostic term such that neonatal hypoglycaemia should be accurately defined as a persistently low blood glucose level, measured with an accurate device, in a baby at risk of impaired metabolic adaptation but with no abnormal clinical signs; or a single low blood glucose level in a baby presenting with abnormal clinical signs (136). To make the definition more
practicable, a group of experts suggested a new concept of “operational thresholds”—the blood glucose thresholds for taking action (137).

Fetuses do not produce glucose under normal conditions and their energy needs are entirely dependent on maternal supply and placental transfer of glucose, amino acid, and free fatty acids, ketones and glycerol (138, 139). After birth and clamping of the umbilical cord, neonatal glucose levels drop quickly and reach a nadir at 1-2 hours of age, then rise to levels that are similar to late gestation fetal concentrations (about two-thirds of normal maternal values) by 2-4 hours, mostly through glycogenolysis and gluconeogenesis. Following that period of rapid change, the neonatal glucose levels rise slowly and reach adult levels in 3-4 days of age (140-142). These glucose changes are vital for promoting glucose production, stimulation of appetite, adaptation to fast/feed cycles and enhancement of oxidative fat metabolism (143). These crucial changes in neonatal glucose levels are modified by several factors including umbilical concentrations of glucose, plasma insulin concentrations, and the onset time and capability of neonatal glucose production (144).

With the occurrence of GDM, fetuses are exposed to hyperglycaemia and develop fetal pancreatic hyperplasia and fetal hyperinsulinaemia, which contribute to neonatal hypoglycaemia after birth (62, 145). Furthermore, the liver is stimulated by glucagon to generate glucose, and this glucagon response appears to be blunted in babies of diabetic mothers (146). In the HAPO study, the authors demonstrated that maternal hyperglycaemia, even under the diagnostic criteria of GDM, was associated with increased risk of clinical neonatal hypoglycaemia (83). Observational studies also
confirmed the relationship between GDM with the increased risk of neonatal hypoglycaemia. Shand and colleagues conducted a population-based study in Sydney, Australia, and they found that the rate of neonatal hypoglycaemia was increased in babies of GDM patients (19.1%) compared to their non-diabetic counterparts (1.6%) (OR 15.07, 95%CI 14.38-15.80) (147). In the United States, Langer and collaborators presented similar results, and showed that infants of GDM patients had increased risk of neonatal hypoglycaemia (6% vs. 2%, OR 2.98, 95%CI 1.84-4.84) (148). However, the rate of neonatal hypoglycaemia is hard to examine in the general population and might be underestimated.

Another cause of neonatal hypoglycaemia is maternal hyperglycaemia during labour, which results in persistent excessive secretion of fetal insulin 1 to 2 hours after birth. Balsells and colleagues found that the capillary blood glucose level of GDM patients during labour was associated with the development of neonatal hypoglycaemia (149). Moreover, previous studies demonstrated that higher maternal pre-gestational BMI, previous GDM history, higher fasting glucose level at diagnosis, and insulin treatment were all associated with increased risk of neonatal hypoglycaemia among babies of GDM mothers (149, 150).

The clinical signs of neonatal hypoglycaemia are not specific; these signs include jitteriness, cyanosis, apnoeic episodes, tachypnoea, a weak and high pitched cry, hypotonia, poor feeding, eye rolling, pallor, hypothermia, sweating, temperature instability, and tachycardia. If the hypoglycaemia is prolonged, more severe signs could be noticed, including changes in level of consciousness (irritability, lethargy, stupor, and
coma), and seizures (151, 152). The literature confirmed that persistent low blood glucose level is associated with acute neurological dysfunction and presents a great risk for cerebral injury (153). The spectrum of cerebral injury includes: white matter injury (parenchymal haemorrhage and ischemic stroke), cortical neuronal injury, and sometimes changes in the basal ganglia (mostly the globus pallidus) and thalami. Posterior parietal and occipital lobes are affected more severely than other regions of the brain (153-155).

Long term neurodevelopmental adverse sequelae following neonatal hypoglycaemia is still controversial (156); the other possible outcomes include milder motor, visual, learning and behavioural problems (157-161). Research also showed that neonatal hypoglycaemia in diabetic pregnancy was associated with worse neurological dysfunction: minimal brain deficits in attention, motor control, and perception, compared to children born to diabetic mothers, but without hypoglycaemia (162).

The treatment strategies include prudent observation of a fetus’s clinical signs, regular blood glucose checking using a proper method, and feeding and/or intravenous glucose infusions (151, 152).

1.4.1.5 Neonatal hyperbilirubinaemia

Bilirubin is a metabolite resulting from the break-down of senescent or haemolysed red blood cells through the reticuloendothelial system. Biliverdin, released from degraded haem, is reduced to bilirubin by biliverdin reductase. This type of bilirubin (unconjugated bilirubin) is water-insoluble and needs to attach to albumin for
transportation via the blood to the liver. Then, in the liver, it is conjugated to glucuronic acid to become more water-soluble. The conjugated bilirubin enters the small intestine and colon and is converted into different forms; most forms will be excreted outside the body through urine and faeces, while others enter the enterohepatic recirculation by reabsorption. Unconjugated bilirubin is highly soluble in lipid, which means it can cross the cell membranes including blood-brain barrier and is toxic to the developing neonatal brain (163, 164).

High levels of bilirubin in the plasma causes yellow discolouration in elastin-rich tissues, including sclera and skin. This phenomenon is known as jaundice. Neonatal jaundice is present in about 60% of term babies and 80% of preterm babies. It could be further divided into two categories, physiological jaundice and the more severe case of pathological jaundice (165). Increased production of bilirubin, deficiency of hepatic uptake, impaired conjugation of bilirubin, and increased enterohepatic circulation of bilirubin are the most common causes of neonatal pathologic jaundice (166). In the most serious cases of hyperbilirubinaemia, neonates could develop acute bilirubin encephalopathy (ABE) and kernicterus, due to neurotoxicity. Symptoms of ABE include lethargy, hypotonia and poor feeding. If this condition is not treated in this stage, it could lead to coma, seizures and, sometimes even death. Kernicterus is the chronic form of bilirubin encephalopathy, characterized by athetoid cerebral palsy, auditory dysfunction, dental-enamel dysplasia, paralysis of upward gaze and intellectual and other handicaps (167-169).
In the HAPO study, the researchers demonstrated that maternal hyperglycaemia was associated with increased risk of neonatal hyperbilirubinaemia, requiring phototherapy (83). Sayin and colleagues found that the rate of neonatal jaundice requiring treatment was higher in the GDM group compared to non-GDM group (17.7% vs. 6.3%, p< 0.001) (170). Similarly, Landon and colleagues indicated the rate of neonatal hyperbilirubinaemia (plasma values greater than 12 mg/dl) was higher in the untreated GDM group compared to the non-diabetic group (14% vs. 2%, OR 3.87, 95%CI 2.64-5.67) (148). The underlying causes of this increased risk among infants of GDM patients include newborn polycythaemia due to fetal hypoxia, the resultant misbalance between increased fetal oxygen consumption that is caused by hyperglycaemia and hyperinsulinaemia, and reduced oxygen supply from the maternal side, that is due to increased maternal haemoglobin affinity of oxygen and reduced placental function, and also the relative immaturity of hepatic bilirubin conjugation and excretion in infants. The higher numbers of broken-down red cells contribute to delivery of extra bilirubin to the immature glucuronosyltransferase enzyme system and results in increased serum unconjugated bilirubin concentration, with a rapid rate of rise followed by a later peak (171). Preterm birth and superficial head bruising due to birth trauma could also exacerbate the situation (172).

The therapeutic options for hyperbilirubinaemia include phototherapy, immunoglobulins for isoimmune haemolytic disease (Rh and ABO haemolytic disease) and exchange transfusion (173).
1.4.1.6 Neonatal respiratory distress

Respiratory distress (RD) is one of the most common neonatal complications after delivery, and its overall incidence rate is around 7%. Among these affected babies, preterm birth has the highest incidence, followed by post-term deliveries (174). RD is defined as any sign of breathing difficulties in the neonates, including tachypnoea (RR >60/min) and tachycardia (HR>160/min), cyanosis, nasal flaring, grunting, apnoea/dyspnoea, and chest wall recession (suprasternal, intercostal and subcostal). There are different pathogeneses of neonatal respiratory distress. The common causes of RD are transient tachypnoea of the newborn (TTN), respiratory distress syndrome (RDS), pneumonia, meconium aspiration syndrome (MAS) and primary or secondary pulmonary arterial hypertension (175, 176).

TTN is now recognized as the main cause of RD in newborns. It is caused by inadequate lung fluid clearance at birth, resulting in excess lung liquid (177). It is generally a self-limiting disorder, and will present with grunting and mild signs of respiratory distress. Usually the symptoms will disappear within 48 hours. However, some of the affected infants will develop an oxygen requirement and will necessitate admittance into the Neonatal unit for a few days (178). The risk factors of TTN include elective and emergency caesarean section, gestational age, birth weight (both low birth weight and high birth weight), maternal age and male sex (179, 180).

A higher rate of TTN among infants of GDM patients has been reported. Persson and colleagues demonstrated that the rate of TTN was doubled among infants of GDM mothers (181, 182). Pinter and collaborators also indicated that fetuses of
diabetic rats had decreased fluid clearance in lung and a lack of thinning of the lung’s connective tissue, which might be the cause of TTN (183). Moreover, increased birth weight, increased rate of caesarean section and increased incidence of preterm birth are all potential explanations for elevated rates of TTN (83). However, other studies found that the rate of TTN was not different between infants of GDM mothers and infants of non-diabetic mothers (170, 184). This inconsistency might be due to the low prevalence of TTN among infants of GDM patients.

RDS, also called hyaline membrane disease, is caused by a deficiency of surfactant (185). The type 2 pneumocytes start to produce surfactant around 24-25 gestational weeks and reach adequate amount to support breathing after birth by 36-37 weeks. The lack of surfactant causes widespread alveolar collapse and results in poorly compliant lungs (186). Normally, infants with RDS present respiratory distress within the first minutes or hours after birth, and most will require respiratory support with oxygen or mechanical ventilation (185).

Babies of diabetic mothers are more likely to suffer from RDS due to two reasons, prematurity and abnormal surfactant production (181, 187, 188). GDM patients have higher incidence rates of preterm birth compared to the general population, which means their babies are at increased risk of developing straightforward surfactant-deficient RDS (189, 190). Furthermore, high blood glucose is involved in several mechanisms that contribute to abnormal production of surfactant, including inhibited surfactant synthesis and secretion by type 2 cells, fewer type 2 pneumocytes/alveolar lining cells and fewer lamellar bodies/alveolar lining cells, blocked trafficking of lipids.
from fibroblasts to type 2 cells, and decreased expression of mRNA for surfactant proteins B and C (191, 192). Thomas and collaborators found that infants of GDM patients had delayed onset of surfactant (phosphatidyl glycerol) compared to babies born to non-GDM women (37.3 ± 0.9 weeks vs. 35.9 ± 1.1 weeks, p<0.001) (193). Researchers have also indicated that maternal glucose control during pregnancy plays an important role in the rate of neonatal RDS; for patients who had well-controlled diabetes, their babies experienced similar lung maturation compared to their non-diabetic counterparts. Babies born to mothers with poorly controlled diabetes showed a significant delay in the appearance of phosphatidyl glycerol (194, 195).

Cardiomyopathy is another cause of RD in infants delivered by diabetic patients. The rate of cardiomyopathy is increased among babies of diabetic mothers with overt diabetes or GDM (196, 197). Fetal hyperinsulinaemia, triggered by maternal hyperglycaemia, increases the synthesis and deposition of fat and glycogen in the myocardial cells and leads to an asymmetric septal enlargement in heart, characterized by increased left ventricular mass and contractility leading to obstruction in the left ventricular outflow tract (198, 199). The infants with cardiomyopathy are usually asymptomatic, but 5-10% of cases have respiratory distress or signs of cardiac dysfunction. Normally, after two to three weeks of supportive care, symptomatic infants recover, and echocardiographic findings resolve within 6 to 12 months (200).
1.4.1.7 Other neonatal short term complications

The increased risk of other neonatal complications, for example, polycythaemia, hypocalcaemia and hypomagnesaemia among infants of GDM patients has been documented, but the prevalence of these complications is relatively low.

1) Fetal hypoxaemia, neonatal polycythaemia, and hyperviscosity

Accumulated evidence indicates that diabetes increases the risk of fetal hypoxaemia during pregnancies (201). It happens more frequently when glucose levels are not well-controlled (202). The exact cause of fetal hypoxaemia is not fully understood. However, there are several potential explanations. Firstly, thickening of the basement membrane of the chorionic villi is more common in diabetic pregnancies, which increases the diffusion distance of oxygen between the mother side and the baby side. Secondly, uncontrolled diabetes could cause decreased uterine blood flow in the placental bed and result in decreased oxygen transfer to the foetus. Thirdly, in GDM patients who have vascular complications (mostly women with unknown pre-existing type 1 or type 2 diabetes prior to pregnancy), pathological changes can be found in the spiral arteries of the placental bed, which narrow the blood flow from the mother to the baby (203-205). Fetal hyperglycaemia and hyperinsulinaemia both contribute to the development of fetal hypoxaemia. Since glucose and insulin are anabolic resources and hormones respectively, they increase oxygen consumption with increased erythropoietin levels in fetal plasma (206, 207). Research has also confirmed the
relationship between the severity of fetal macrosomia and the risk of fetal chronic hypoxia (208).

Chronic fetal hypoxaemia can lead to cord blood acidosis, low Apgar scores, reticulocytosis and, in the worst case, perinatal death (209). The best method to avoid fetal hypoxaemia is still under discussion. However, one commonly used method is intensive fetal monitors, including biophysical profile, doppler blood flow measurements and non-stress testing (210, 211). There are also guidelines that recommend ending pregnancy before term to avoid unpredictable perinatal death (212).

Neonatal polycythaemia is defined by a venous haematocrit (hct) that exceeds normal values for gestational and postnatal age by two standard deviations (213). For a term infant, polycythaemia is diagnosed if the hct from a peripheral venous sample is greater than 65% or the haemoglobin in greater than 22 g/dl (214).

The incidence of polycythaemia is 1.5-4% in the general population and the risk factors include fetal transfusions, intrauterine hypoxia and other rare fetal causes such as Beckwith Weidemann syndrome (214, 215). Infants of diabetic mother have higher risk, about 10% to 30%, of developing polycythaemia compared to babies of non-diabetic mothers (216-218). The underlying pathogenesis of this higher incidence might be the increased erythropoietin concentration caused by chronic fetal hypoxemia (82).

Hyperviscosity, normally caused by polycythaemia, is defined as a viscosity greater than 14.6 centipoise, at a shear rate of 11.5 reciprocal seconds. It can lead to different symptoms including intravascular aggregation, ischaemia, and infarction of vital organs (219).
2) Neonatal Hypocalcaemia

In the human body, calcium exists in two places: skeleton (99%) and extracellular fluid (1%). There are three different forms of calcium in the extracellular fluid: calcium bound to albumin (40%), calcium bound to anions like phosphorus, citrate, sulphate and lactate (10%) and free ionized calcium. Ionized calcium is a crucial element for many important biochemical processes, such as neuromuscular excitability, coagulation, cell membrane integrity and function, as well as cellular enzymatic and secretory activity; it is tightly regulated by parathyroid hormones and vitamin D levels. Elevated extracellular pH in cases such as acute respiratory alkalosis, could increase the binding of calcium to albumin, which decreases the concentration of ionized calcium without affecting the total serum calcium level (217, 218).

In the third trimester, fetal serum calcium (SCa) is higher than the mother’s SCa, and is actively transferred from the maternal side to the fetal side. After birth, neonatal SCa starts to decrease and reaches a nadir of 7.5-8.5 mg/dl (1.9-2.1 mmol/l) in healthy term babies in two days (220). However, PTH levels increase gradually in the first 48 hours of life and determine similar levels of SCa are seen in older children and adults by two weeks of age (221).

Neonatal hypocalcaemia is defined as a total serum calcium level below 1.75 mmol/l or ionized calcium less than 1 mmol/l in preterm babies. In term infants, the diagnostic criteria are total serum calcium below 2 mmol/l or ionized calcium less than 1.2 mmol/l. It can be divided into two categories: early onset neonatal hypocalcaemia
(ENH), that is relatively common and occurs within the first 3-4 days of life, and late onset neonatal hypocalcaemia (LNH), that is rare and usually presents at the end of the first week of life. Prematurity, infants of diabetic mother, perinatal asphyxia, maternal hyperparathyroidism and intrauterine growth restriction are the common causes of EMH. The reasons for developing LNH include hypomagnesaemia, high phosphate load, hypoparathyroidism, vitamin D deficiency states, and iatrogenic cause.

The clinical presentations of neonatal hypocalcaemia vary widely. Some cases are asymptomatic, others may present non-specific symptoms (apnoea, cyanosis, tachypnoea and vomiting). In some cases, neuromuscular symptoms (myoclonic jerks, jitteriness, exaggerated startle, tetany and seizures) and cardiac abnormalities (tachycardia, prolonged QT interval, decreased contractibility and heart failure) are also observed. Calcium supplementation for at least 72 hours is the regular treatment for EMH, and usually will resolve hypocalcaemia in 48-72 hours without any significant sequelae. The therapy for LNH is longer and more complicated, based on the aetiology; in the most severe cases, babies with LNH may need lifelong treatment (221, 222).

Diabetes increases the risk of hypocalcaemia in newborns; hypocalcaemia occurs in 10%-20% of babies of mothers with diabetes, including overt diabetes and GDM (223, 224). This may be related to the increased calcium demands of a macrosomic baby, as well as maternal hypomagnesaemia caused by magnesium depletion in diabetic mothers, combined with functional hypoparathyroidism in infants (225). The higher risk of birth asphyxia and prematurity might also contribute to the increased risk of hypocalcaemia in babies of diabetic mothers. Recent research demonstrated that
infants of GDM patients have specific calcium sensing receptor genotype that is associated with decreased calcium levels both at birth and on the 2\textsuperscript{nd} day of life (226). Strict management of diabetes in pregnancy might reduce the risk of neonatal hypocalcaemia (227).

3) Neonatal Hypomagnesaemia

During pregnancy, maternal serum magnesium (Mg) levels decrease, combined with a 25\% increase of renal Mg excretion. Diabetes will further exacerbate urinary loss of Mg, particularly the intracellular free magnesium level, which may cause neonatal hypomagnesaemia (228, 229). Little is known about fetal magnesium homeostasis. Animal studies show that the materno-fetal flux of magnesium is reduced in the presence of maternal diabetes mellitus (230).

Neonatal hypomagnesaemia, defined as less than 0.02 mmol/l might have an increased rate among infants of diabetic mothers within the first three days after birth. Prematurity and pregnancy complicated with preeclampsia will increase the risk of developing hypomagnesaemia (231, 232). Neonatal hypomagnesaemia is usually transient and asymptomatic; however, there are also severe cases with different manifestations, including neuromuscular hyperexcitability (e.g. tetany, convulsions), cardiovascular symptoms (e.g. changing in ECG, atrial and ventricular arrhythmias), and hypokalaemia (233, 234). It can also reduce both parathyroid hormone (PTH) secretion and PTH responsiveness. Thus, for neonates that have both hypomagnesaemia and
hypocalcaemia, the treatment for hypocalcaemia might not work until the hypomagnesaemia is corrected (85, 235).

1.4.2 Maternal short term complications

1.4.2.1 Hypertension disease induced by pregnancy

Hypertension is a common maternal complication during pregnancy and is associated with increased maternal and neonatal mortalities and morbidities. They can generally be divided into four categories: 1) Chronic hypertension: hypertension that was present at <20 weeks gestation that does not progress to preeclampsia. 2) Gestational hypertension: a systolic blood pressure ≥ 140 mm Hg and/or a diastolic blood pressure ≥ 90 mmHg on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with previously normal blood pressure. 3) Preeclampsia: hypertension after 20 weeks of gestation associated with proteinuria of ≥ 300 mg per 24 hours or ≥1+ dipstick. Preeclampsia is also diagnosed as hypertension in association with thrombocytopenia, impaired liver function, new development of renal insufficiency, pulmonary oedema or new-onset cerebral or visual disturbances, even in the absence of proteinuria. 4) Chronic hypertension with superimposed preeclampsia: chronic hypertension combined with the symptoms of preeclampsia that develop after 20 gestational weeks (236-238). There are also more severe types of pregnancy-induced hypertension such as eclampsia (hypertensive patients with convulsions during pregnancy or in the first 10 days postpartum) and HELLP syndrome (a syndrome characterized by Haemolysis, Elevated Liver enzymes and a Low Platelet count).
However, their prevalence is quite low, around 0.27% and 0.8% among all the pregnant women, respectively (239, 240).

Approximately 10% of women have gestational hypertension during pregnancy. For preeclampsia, the prevalence is around 2-8% depending on the studied population (241). Maternal adverse outcomes associated with hypertensive disorders include increased caesarean deliveries, abruptio placentae, renal failure, stroke, cardiac arrest, adult respiratory distress syndrome, coagulopathy and liver failure. It also increases the risk of developing perinatal morbidities, including fetal growth restriction, prematurity, and respiratory distress syndrome after birth (242, 243).

Gestational diabetes is associated with increased risk of pregnancy-induced hypertension including gestational hypertension and pre-eclampsia, even after adjustment for body mass index, age, ethnicity, parity and prenatal care (244-247). In the HAPO study, authors indicated that maternal hyperglycaemia was associated with increased risk of preeclampsia (83). In a large Australian population-based study, Shand and colleagues demonstrated that GDM patients had increased risk of gestational hypertension (6.9% vs. 4.2%, OR 1.74, 95%CI 1.64-1.85) and preeclampsia (6.7% vs. 4.4%, OR 1.63, 95%CI 1.53-1.74) (147). Accumulated evidence indicates that this association, at least in part, could be due to insulin resistance (248-250). A secondary analysis of the HAPO study proved that higher fasting C-peptide, an acceptable measure of insulin sensitivity in pregnancy if patients have normal insulin secretory capacity, is an independent risk factor of preeclampsia, after being adjusted for BMI and fasting glucose (251).
The underlying mechanisms between insulin resistance and gestational hypertension are not fully understood. However, it is believed that insulin resistance could cause hypertension at cellular, circulatory and neurologic levels. In the sympathetic nervous system, insulin resistance stimulates the release of plasma norepinephrine and reduces the capacity of vasodilation. At the circulatory level, hyperinsulinaemia can cause hypertrophy of the vascular smooth muscle cells and vasoconstriction. Hyperinsulinaemia also has an effect on the cellular membrane pump, and can increase intercellular calcium and vascular tone (252).

Independent of insulin resistance, hypertension could also be induced by functional abnormalities of the vascular endothelium that results from maternal hyperglycaemia. Hyperglycaemia increases the concentration of free radicals and advanced glycosylation endproducts, which reduce the availability of NO for vasodilation (253, 254). Placental abnormalities, such as plethora, chorangiosis, and a relatively immature villous structure, happen more frequently in diabetic mothers, and could lead to the release of different vasoactive and pro-inflammatory substances (α-TNF, leptin, etc.), that are related to the development of gestational hypertension (255-257). Finally, gestational diabetes could cause dyslipidaemia, characterized by increased oxidized low density lipoprotein (LDL) that can inactivate endothelial nitric oxide (NO) and cause vascular dysfunction (254, 258, 259).

Several randomized controlled trials have found that strict treatment of GDM could reduce the risk of developing pregnancy-induced hypertension during pregnancy. The Australian Carbohydrate Intolerance Study in Pregnant Women (ACOIS) found a
lower incidence of preeclampsia in the treated group compared to the routine-care group (12% vs. 18%, p=0.02)(260). Similarly, Landon and colleagues indicated that treatment reduced the risk of pregnancy-induced hypertension, both for gestational hypertension and preeclampsia, in GDM patients (8.6% vs. 13.6%, p=0.01) (261).

1.4.2.2 Preterm Birth

Preterm birth is defined as birth occurring before 37 weeks of completed gestation. An estimated 10% of all births worldwide are preterm, which means around 41,000 infants are born before term each day (262). In a comprehensive systematic review, authors indicated that most countries have shown an increase in preterm birth rates over the last 20 years (263). In Australia, the risk of preterm birth increased from 5.5% in 1991 to 7.5% in 2011: 0.8% pregnant women gave birth at 20-27 weeks, 0.7% at 28-31 weeks, and 6.0% delivered at 32-36 weeks (264, 265).

Preterm birth can be divided into two categories depending on the clinical presentation: spontaneous preterm birth (which contemplates either spontaneous onset of labour with intact membranes, or after preterm premature rupture of membranes - PROM), and medically-indicated preterm birth for maternal or fetal indications. This includes maternal preeclampsia, fetal distress, SGA, and placental abruption. It is estimated that around 2/3 of all preterm births are spontaneous (266).

Preterm birth is associated with increased perinatal mortality, as well as short- and long-term morbidities. It is known that the risk of adverse consequences decline with increasing gestational age (267). In Australia, the rate of neonatal death
was 410 per 1000 births for infants born <28 weeks, but decreased exponentially to 30 per 1000 birth for infants born at 28-31 weeks, and 4.7 per 1000 for infants born at 32-36 weeks. However, even the lowest mortality rate of babies born preterm at 32-36 weeks is still five times higher than mortality for infants born after 37 weeks (268). Other countries show similar trends (269). Compared to term-born babies, preterm born infants had increased risk of respiratory distress, infection, hypothermia, hypoglycaemia, hyperbilirubinaemia, hypoxic-ischaemic encephalopathy (HIE), intraventricular haemorrhage and feeding problems. Necrotizing enterocolitis and retinopathy have also been reported, although they are more common in the infants born extremely preterm (< 28 weeks) (267, 270, 271). Infants born preterm experience long-term complications, such as an increased risk of cerebral palsy, developmental coordination disorder, visual impairment, hearing impairment, cognitive impairment, and neurobehavioral disorders (272, 273).

The HAPO study also confirmed that an increased risk of preterm delivery is associated with elevated 1h OGTT results (OR 1.18 95% CI 1.12-1.25), and 2h OGTT results (OR 1.16 CI 1.10-1.23) but not for the fasting OGTT result (OR 1.05 95%CI 0.99-1.11) after being adjusted for confounders (83). Yang and colleagues found that patients who had impaired glucose tolerance during pregnancy with conventional obstetric care, had increased risk of preterm birth (OR 6.42 95%CI 1.46-28.34) (274). In a large population-based cohort study including 1,260,297 women with singleton pregnancies in Sweden, researchers demonstrated that GDM patients had a higher risk of preterm birth (8.6% vs. 5.0%, adjusted OR 1.71, 95% CI 1.58-1.86) (84).
It is important to note that these studies did not separate spontaneous preterm birth from medically-induced preterm birth. The increased rate of preterm birth may be attributed to the higher risk of indicated preterm birth, caused by increased risk of preeclampsia in GDM patients. There were inconsistent results regarding the relationship between GDM and spontaneous preterm birth (sPTD). Jensen and co-workers found that despite treatment, an increased risk of sPTD is associated with higher 2h OGTT results, either between 9.0-11.0 mmol/l (OR 2.0 95% CI 1.0-3.6) or ≥11.0 (OR 5.1 95%CI 2.4-11.0) (275). Similar results were confirmed by Lao and colleagues (275). They demonstrated that the incidence of sPTD correlated significantly with increasing glucose intolerance in diet-treated GDM patients; the rate of sPTD increased from 5.5%, in patients whose 2h OGTT results were 5.9 mmol/l or less, to 10.3%, in patients whose 2h OGTT results were 11.0 mmol/l or greater (276). Conversely, Yogev and collaborators conducted a retrospective study, and concluded that the rate of sPTD was similar between GDM and non-GDM patients (10.7% vs. 11.7%, p=0.20). However, they indicated that sPTD patients in their research had a higher mean blood glucose result in the OGTT (114± 16 mml/l vs. 106± 14 mml/l, p= 0.001), and a lower proportion of patients with well-controlled glucose levels (35% vs. 54%, p= 0.004), when compared to GDM patients who had term birth. GDM patients who had sPTD were likely to have fewer prenatal visits, although the result was not statistically robust (6.2± 1.3 times vs. 7.7 ± 2.2 times, p= 0.08). Moreover, the rate of insulin use was comparable between GDM patients who had preterm deliveries and GDM patients who had term birth (47% vs. 50%, p= 0.22) (277). Bar-Hava and colleagues also demonstrated that the incidence of sPTD among GDM patients was similar to the non-diabetic population (6.2% vs. 6.5%,
p = 0.82). They also stated that there was no statistical difference in the proportion of patients who had poor glycaemic control, defined as a mean blood glucose level higher than 6.1 mmol/l, between GDM patients who had sPTD and GDM patients who had term birth through the entire treatment period (26.6% vs. 31.2%, p = 0.83), as well as the week preceding delivery (40% vs. 17.9%, p = 0.28). However, patients in this study generally had relatively good glucose control, based on their low mean blood glucose, which might explain the inconsistent results. Moreover, the sample size in this study was also relatively small (34 sPTD patients) (278).

In conclusion, the overall rate of preterm birth is increased among GDM patients. It is still controversial whether GDM patients have an increased risk of spontaneous preterm birth. However, the rate of sPTD might be associated with the severity of glucose intolerance and glucose control during pregnancy.

1.4.2.3 Rate of caesarean section (CS)

Caesarean section is defined as the delivery of a baby through surgical incision in the abdomen and uterus. It is also known as an intervention used to reduce the risk of obstructed labour and the adverse complications associated with it, such as shoulder dystocia (279). Just like any surgical procedure, CS has its own side effects. For mothers, it is directly associated with several unpleasant outcomes, including wound infection and dehiscence, postpartum infection, postpartum haemorrhage, urinary and gastrointestinal injuries and deep venous thrombosis (280, 281). Furthermore, CS for a current pregnancy, increases the likelihood that CS will become necessary in subsequent
pregnancies, and increases the risk of malpresentation, placenta praevia, antepartum haemorrhage, placenta accreta, prolonged labour, uterine rupture, small for gestational age babies, and in the worst case scenario, unexplained stillbirth (282). There are also fetal risks related to CS. The incidence of transient tachypnoea of the newborn born was about three times higher among babies born to CS compared to those who went through vaginal birth (283). The increased risk of respiratory distress syndrome was also reported among neonates after CS; however, having labour before CS lowers the risk of respiratory distress syndrome. The OR was 2.6 (95% CI 1.3 – 2.8) without labour and 1.9 (95%CI 2.2-2.9) with labour (284, 285). Children born to CS may have a higher risk of developing allergies, asthma, type 1 diabetes and malignancies in the future (286).

Evidence from different studies indicate that untreated GDM increases the risk of CS. Langer and colleagues demonstrated that the overall risk of CS increased 2-fold for untreated GDM patients, compared to non-diabetic mothers, and the risk was further increased to 4-fold for GDM patients with LGA babies (148). Similar results were demonstrated by Naylor et al in the Tri-Toronto Hospital Gestational Diabetes Project. They found the rate of CS in the untreated GDM group was higher than in the normoglycaemic controls (29.6% vs. 20.2%, p=0.02) and this increase could be attributed to the increased rate of macrosomia (28.7% vs. 13.7%, p<0.001) (287). The most decisive evidence comes from the HAPO study; the authors found that after adjustments for maternal BMI and other confounders, elevated fasting glucose level (OR 1.11 95% CI 1.06-1.15), 1-hour glucose level (OR 1.10 95%CI 1.06-1.15), 2-hour glucose level (OR 1.08 95%CI 1.03- 1.12) were all related to increased risk of primary CS. Importantly, in the
HAPO study, the results of OGTT were blinded to both the care providers and the patients, which excluded the influence of subjective bias on decision making, as well as the patients themselves (81).

However, the relationship between treated GDM and the rate of CS is still controversial. Landon and collaborators conducted a large randomized study to examine the effects of GDM treatments. They demonstrated that GDM treatment could reduce the risk of CS among GDM patients (26.9% vs. 33.8%, p=0.02) (261). However, in another study assessing the efficacy of GDM treatment, Crowther and colleagues found that the risk of elective CS was comparable between GDM patients who received intervention and GDM patients who had routine care (15% vs.12%, p= 0.33), as well as the rate of emergency CS (16% vs.20%, p= 0.31) (288). Moreover, Naylor et al demonstrated that although treatment of GDM normalized the babies’ birth weights, the rate of CS was still increased after adjustments for potential confounders (OR 2.1 95% CI 1.3-3.6) when compared to the normoglycaemic controls, and the risk was comparable to the untreated group (33% among treated GDM patients vs. 29.6% among un-treated GDM patients). The author concluded that the awareness of GDM may lower the threshold for surgical delivery (287). Similar results were found in a recent study; Gorgal et al demonstrated that patients treated for GDM have an increased risk of having non-elective CS compared to glucose tolerant women after adjustments for maternal age, pre-pregnancy BMI, gestational weight gain, previous caesarean section, gestational age at delivery and birth weight (adjusted RR 1.52 CI 1.06- 2.16). Given the similar rates of fetal distress and failure to progress in both GDM patients and the control group,
researchers suggested that GDM might modify obstetrical practice and increase the risk of CS (289).

In conclusion, the rate of CS is increased among untreated GDM patients. Whether the treatment of GDM could reduce the risk of CS was controversial. However, awareness of GDM might lower the threshold for CS.

1.4.2.4 Other maternal complications during pregnancy

There is increased risk of other maternal complications during pregnancy, for example, operative vaginal delivery and psychological problems. However, these complications have not been fully analysed and are less frequently reported in the literature.

1) Operative vaginal delivery

Operative vaginal delivery was defined as the application of forceps or vacuum extractors during the second stage of labour (290). The association between operative vaginal delivery (OVD) and GDM has not been comprehensively analysed. Kristina et al found a comparative risk of OVD between untreated GDM patients and non-diabetic women (19% v.s.19%, p> 0.05) (291). In another study that compared the outcomes of glucose-tolerant women with patients who had gestational impaired glucose tolerance (a fasting glucose level <6.7 mmol/l and a 2-h glucose level of the OGTT in the 9.0-11.0 mmol range) but were not treated, the risk of OVD was also similar between the two groups (7.5% vs. 7.9%, p>0.05) (184). Similar results were reported in
terms of the risk of OVD among GDM patients with treatment. Svare et al demonstrated a comparable rate of OVD between treated GDM patients with non-diabetic women (7% vs. 10%, p>0.05) (292). However, there are also contradictory results in the literature. In a recent large population-based cohort study conducted in Sweden, authors found that the rate of OVD was lower in the treated GDM group, compared to non-diabetic women (5.5% vs.6.6%, p<0.001) (84). Conversely, in an Australian population-based study, authors found that the risk of OVD was higher in the treated GDM group compared to non-diabetic women after adjustment for the high prevalence of macrosomia (28.7% vs. 41.0%, OR 1.4, 95% CI 1.4-1.7) (293).

Furthermore, GDM was associated with an increased risk of failure in OVD. Sameer et al conducted a population-based case control study to determine the risk factors of failed OVD. They demonstrated that, after controlling for macrosomia, GDM was still associated with an increased risk of failed OVD (OR 1.54 CI 1.13- 2.10) (294).

2) Perineal injuries

Perineal injuries are classified into degrees, depending on the anatomical structures involved, from first degree (injury to perineal skin only) to fourth degree (injury to perineum involving the anal sphincter complex and anal epithelium) (295). The relationship between GDM and perineal injuries is controversial. In a population study in Australia, the authors found that the risk of third and fourth degree perineal tears were higher among GDM patients compared to non-diabetic women (1.9% vs. 1.3%, OR 1.43, 95%CI 1.24-1.65) (147). Similarly, in Saudi Arabia, researchers found an increased
risk of perineal lacerations in GDM patients compared to non-GDM women (18% vs. 10.7%, p<0.001) (296).

However, this association was not confirmed in other studies. Adams demonstrated comparable risk of rectal injury between women with unrecognized GDM and non-diabetic women (291). In the Toronto Tri-hospital Gestational Diabetes Project, researchers also demonstrated that there was no statistical difference in terms of the risk of perineal injuries between treated GDM patients and non-diabetic controls (287).

3) Post-partum Haemorrhage

Post-partum Haemorrhage is normally defined as maternal blood loss more than 500 ml within the 24 hours following childbirth (297). The relationship between GDM and post-partum haemorrhage has not been fully evaluated. According to a recent large population-based cohort study in Denmark, post-partum haemorrhage was similar between the GDM group and the non-GDM control population (298). In Australia, researchers demonstrated that the risk of post-partum haemorrhage was comparable between GDM patients and non-GDM women (6.3% vs. 6.0%, OR 1.06, 95%CI 0.99-1.13) (147).

Similarly, the treatment of GDM did not reduce the risk of post-partum haemorrhage. Crowther et al. found that the rate of post-partum haemorrhage (> 600 ml) was comparable between the intervention GDM group and the routine-care GDM group (6% vs. 6%, p=0.86) (288). There is no difference in the risk of post-partum
haemorrhage between GDM patients who were treated with metformin and patients who were treated with insulin (299).

4) Psychological problems

A diagnosis of GDM has a significant influence on women’s perception of health, pregnancy experience and may create psychological problems. Nolan et al interviewed women who had type 2 diabetes and GDM during pregnancy, and demonstrated three primary themes regarding their health concerns, including concern for the infants, concern for self and sensing a loss of personal control over their health (300). Rumbold and co-workers conducted a survey to evaluate the experience of pregnant women after being screened for GDM. They found that patients who had positive screen results had lower health perceptions (p< 0.005), were less likely to rate their health as “much better than one year ago” (p<0.005) and were more likely to only rate their health as “fair” compared to pregnant women who had negative results. However, no differences were found in levels of anxiety or depression between the two groups (301). An American study indicated that GDM diagnosis was associated with an increased level of anxiety and depression throughout pregnancy and six weeks postpartum (302). Interestingly, in a longitudinal prospective study, researchers found that the GDM group had significantly higher anxiety scores at the beginning of the treatment for GDM, but the scores became comparable to the non-diabetic group at 36 weeks or 6 weeks postpartum (303). Researchers from the Australian Carbohydrate Intolerance Study in Pregnant Women (ACOIS) also revealed that glucose intolerant
patients who underwent intensive intervention had lower rates of depression and improved health-related quality of life, compared to those who had routine obstetric care (304).

The results regarding the patients’ experiences of treatment were inconsistent. Carolan and colleagues found that most GDM patients spoke of the challenge of implementing a complex regimen of blood testing and dietary manipulation within a very short time frame, while they were still in shock from the GDM diagnosis. Instead, GDM patients found treatment via the use of insulin an easier option, compared to dietary control alone. They were happy to start insulin treatment as they felt that it made their task more achievable (305). Conversely, Melinda and collaborators indicated that GDM patients treated with insulin were more likely to experience shock, fear or anxiety (306).

1.5 Long term complications of GDM

There is an increased risk of developing metabolic abnormalities, cardiovascular problems and other diseases among GDM patients and their offspring.
1.5.1 Neonatal long term complications

1.5.1.1 Metabolic abnormalities: obesity, type 2 diabetes, and metabolic syndrome

The association between maternal diabetes during pregnancy and increased risk of metabolic abnormalities in offspring has been demonstrated by a number of studies, using various methodologies. A study focused on the Pima Indians of the Arizona population, who had very high levels of obesity, type 2 diabetes and gestational diabetes, provided convincing evidence of the aforementioned link between maternal diabetes and metabolic abnormalities in offspring. Diabetic diseases during pregnancy include pre-existing type 1 and type 2 diabetes and gestational diabetes, and gestational diabetes accounts for the majority (about 88% gestational diabetes, 7% type 1 diabetes and 5% type 2 diabetes) (307). In this population, babies of diabetic mothers had a higher prevalence of obesity at 15 to 19 years of age, as compared to babies of pre-diabetic and non-diabetic mothers, even for the babies who had normal birth weight (307, 308).

In order to exclude genetic and postnatal maternal lifestyles influence, sibling studies were performed. Offspring of diabetic mothers showed higher mean BMI and risk of type 2 diabetes compared to their siblings born before their mothers were diagnosed with diabetes. Further, there was no association between paternal diabetes around the time of their partner’s pregnancy and the offspring’s BMI or the risk of diabetes (308). These results showed that in the Pima Indian population, the increased
risk of obesity and diabetes in the offspring of diabetic mothers was at least partially due to intrauterine exposure mechanisms.

This association has also been confirmed by studies in other populations. In a large epidemiologic study including more than 280,000 Swedish males, the authors found an average 0.94 kg/m$^2$ BMI higher in subjects whose mother had either GDM or overt diabetes during their pregnancy, compared to their brothers born before their mothers were diagnosed with diabetes (309). A recent study analysed the relationship between maternal GDM and female offspring adiposity. The results indicated that maternal GDM increased the risk of childhood adiposity in female offspring. Moreover, the risk of adiposity was also increased if the mother was overweight (310).

Metabolic syndrome is defined as central obesity, plus any two of four additional factors: elevated triglyceride level, reduced HDL-cholesterol, hypertension/elevated blood pressure, or elevated fasting plasma glucose (311). In Pima Indians, a diagnosis of diabetes in the mother was strongly associated with elevated systolic blood pressure in the offspring (312). In another study in Denmark, researchers compared adult offspring of women with diet-treated GDM, women with type 1 diabetes and offspring from the normal population, and found that the risk of metabolic syndrome increased 4-fold in the offspring of GDM mothers and 2.5-fold in the offspring of mothers who had type 1 diabetes. The offspring’s risk of the metabolic syndrome increased in parallel with increasing maternal fasting blood glucose and 2-h blood glucose (313). However, in an American study, researchers demonstrated that only the LGA offspring of diabetic mothers had an increased risk of metabolic syndrome in
childhood; this increased risk was not found in LGA offspring of non-GDM mothers, appropriate-for-gestational age (AGA) offspring of GDM mothers and AGA offspring of non-GDM mothers (314).

Epigenetic modifications may explain the association between maternal diabetes during pregnancy, and increased risk of metabolic disease of the offspring in their later lives, since such modifications are generally assumed to moderate gene-environment interactions (315). Among these modifications, DNA methylation of specific sequences is best understood. The affected genes include the leptin gene promoter (316), the adiponectin gene promoter (317), mesoderm-specific transcript (MEST) (318) and others. Research also showed that reduced circulating cord blood endothelial colony-forming cell (ECFC) numbers and premature ECFC senescence may predispose infants born to diabetic mothers to develop endothelial dysfunction and hypertension (319).

1.5.1.2 Cognitive ability

Whether maternal pregnancy diabetes will adversely affect offspring cognitive development is still controversial. The offspring of diabetic mothers, not specific the type of maternal diabetes, were found to have higher rate of memory deficits (age 1) (320), higher rate of attention deficits, lower cognitive scores, lower gross and fine motor achievements at younger age (321), higher army rejection rates (322), higher risk of not completing compulsory schooling (age 16) (323), and lower IQ score (age 9)(324). Aberrant lipid metabolisms, such as third-trimester plasma β-
hydroxybutyrate and free fatty acid in GDM mothers were found to be associated with poorer intellectual performance and psychomotor development in offspring (325).

However, researchers in India failed to prove the association between maternal GDM and poorer cognitive ability in their offspring, when assessed for learning, reasoning, verbal ability, attention, and concentration (326). Interestingly, in a Swedish sibling study, subjects whose mother had pregnancy diabetes had, an IQ that was lower on average than subjects whose mothers did not have diabetes in pregnancy (OR -1.36, 95% CI -2.12, -0.60), in non-siblings. But in siblings, offspring exposed to maternal diabetes in pregnancy did not show a significant difference in IQ score compared to their non-exposed siblings. This finding suggested that exposure to diabetic milieu could not fully explain the observed decrease in offspring cognitive abilities (327).

1.5.1.3 Other complications

Researchers found an increased risk of malignant neoplasm in children prenatally exposed to maternal type 2 diabetes, but found no relation to paternal diabetes. The authors suggested the risk of malignant neoplasm later in life may to some extent be programmed by a suboptimal intrauterine environment associated with maternal diabetes (328). Similarly, studies showed an increased risk of hospitalization for neoplasms in children (up to 10 years old) born to the mothers who had pre-existing diabetes, but no increased risk was observed for children of GDM mothers (329).
Researchers also indicated that children born to GDM mothers (OR 1.20 95% CI 1.11-1.28), and children born to the mothers who had pre-existing diabetes (OR 1.56 95% CI 1.43-1.70) had an increased risk of being hospitalized for infections (329).

In Pima Indians with type 2 diabetes, their offspring had a higher prevalence of elevated urinary albumin excretion (UAE) (58%), compared to the offspring of prediabetic mothers (i.e. not diabetic at the time of the pregnancy but whom developed diabetes after pregnancy) (43%), and also the offspring of non-diabetic mothers (40%). This result suggested that the diabetic intrauterine environment might be independent of other susceptibility factors that may lead to nephropathy (330).

**1.5.2 Maternal long term complications**

**1.5.2.1 GDM recurrence**

The recurrence rate of GDM is high, and previous studies have found rates that ranged from 35% to 69%. In a retrospective Canadian study, authors found a 35.6% recurrence rate of GDM between 1980 and 1996. Infant birth weight in the index pregnancy and maternal pre-pregnancy weight before the subsequent pregnancy were predictive factors in multivariate regression analysis (331). An American study indicated that the risk of GDM in the second pregnancy among women with previous GDM was higher, compared to those without previous GDM (adjusted OR 13.2 95% CI 12.0 – 14.6). For the third pregnancy, the highest rate of recurrence was found for patients whose first and second pregnancies were all complicated with GDM (adjusted OR 25.9 95% CI 17.4- 38.4), which means the magnitude of recurrence risk increased with the number
of prior episodes of GDM. Researchers also found that Hispanics and Asian/Pacific Islanders had a higher risk of GDM recurrence, compared to other ethnicities (332). In Australia, a recent study presented a similar rate of GDM recurrence (41.2%). Authors concluded that a maternal age over 35 years old, particular ethnicities (Middle East/North Africa and Asia), pregnancy hypertension, LGA in infants, preterm birth in the first pregnancy, longer inter-pregnancy period, and multiple pregnancies in the second pregnancy were all independent predictors of GDM recurrence (333). Higher rates of GDM recurrence was reported by Spong et al and Major et al, 68% and 69% respectively (334, 335).

1.5.2.2 Type 2 diabetes

GDM history can increase the risk of developing type 2 diabetes in the future. A comprehensive meta-analysis including 20 studies and 675 455 women (10 859 with type 2 diabetes) concluded that women with previous gestational diabetes had at least a seven-fold increased risk of developing type 2 diabetes in the future, compared to women without GDM history. The risk ratio was generally consistent after controlling for ethnicity, follow-up time, study design, BMI at index pregnancy, and follow-up BMI (336). The elevated pre-pregnancy BMI, later GDM diagnosis and insulin requirement during pregnancy were all risk factors for the development of type 2 diabetes in the future (337). Further, Kim et al concluded in another systemic review that the cumulative incidence of type 2 diabetes increased markedly in the first 5 years after delivery and appeared to plateau after 10 years. Higher fasting glucose level during
pregnancy was the most common risk factor for the development of type 2 diabetes (338).

All these risk factors potentially represent the magnitude of the insulin resistance, which is a hallmark of developing future diabetes (339). The association between GDM and type 2 diabetes has also been supported by genetic analysis. Some of the type 2 diabetes-associated genetic variants were also associated with GDM (340, 341).

1.5.2.3 Cardiometabolic abnormalities

Women with previous GDM history had a higher risk of developing metabolic abnormalities, as well as cardiovascular problems. A recent large meta-analysis, including more than 5000 participants (2520 cases and 3312 control) confirmed that women with GDM history had almost 4-fold higher risk of developing metabolic syndrome (OR 3.96 95% CI 2.98 – 5.26). Interestingly, Caucasian women demonstrated a significantly higher chance of having metabolic syndrome after pregnancy complicated with GDM than Asian patients (Caucasian OR 4.54 95% CI 3.78 – 5.46; Asian OR 1.28 95% CI 0.64 – 2.56). Further, the author found that GDM patients with higher BMI were more likely to develop metabolic syndrome compared to the BMI matched group (higher BMI OR 5.39 95%CI 4.47 – 6.50; matched BMI OR 2.53 95% CI 1.88 – 3.41) (342).

To examine the association between GDM history and future cardiovascular disease, a scoping review was performed, which included 11 studies until mid-2012. In the review, the author stated that previous GDM history is associated with an increase
in the risk of cardiovascular disease; however, this association disappeared after adjustments for subsequent diagnoses of diabetes (343). Recently, Fadl et al and colleagues conducted a large population-based case-control study in Sweden. They found that previous GDM history increased the risk of cardiovascular disease 1.5-fold (95% CI 1.07-2.14) after being adjusted for common risk factors for cardiovascular disease, including chronic hypertension, smoking, BMI, education level, parity and ethnicity. However, a diabetes diagnosis after pregnancy presented an even higher risk for cardiovascular disease (OR 4.8 95% CI 3.23-7.13). The association between GDM history and cardiovascular disease lost statistical significance after adjustments for postpartum diabetes, excepted for women who were overweight or obese (344).

Inflammation that is associated with insulin resistance may be a potential link between GDM history and subsequent cardiometabolic disease (345). Research indicates that high levels of C-reactive protein (CRP) is the mark of cardiometabolic diseases (346, 347). Recently, osteoprotegerin (OPG), a soluble member of the tumour necrosis factor receptor superfamily that increases inflammation has been linked with both cardiovascular disease (348) and metabolic syndrome (349) and further confirmed the relationship between inflammation and cardiometabolic abnormalities. Further, research found that small artery function was impaired at 2 years postpartum, in women with abnormal glucose levels during pregnancy (350).
1.6 GDM treatment

1.6.1 Rationale for treatment

As indicated in the HAPO study, higher maternal plasma glucose levels are associated with adverse maternal and neonatal complications such as pregnancy-induced hypertension, macrosomia, and neonatal hypoglycaemia (83). In spite of an accumulation of evidence indicating that abnormal lipid profiles of GDM women may also play a role in causing these complications, there is still a lack of specific treatments for this pathological pathway. The current treatment strategies mainly tackle maternal hyperglycaemia through self-monitoring of glucose, diet and exercise, and, if needed, pharmaceutical treatment. Several large randomized clinical trials have confirmed the effectiveness of GDM treatment. The Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) trial was published in 2005. It included 1000 patients with mild glucose intolerance who were randomly assigned to receive dietary advice, blood glucose monitoring and insulin therapy if needed (the intervention group) or routine care in which mothers and their treating clinicians were blinded to the abnormal glucose tolerance. The researchers showed that patients in the intervention group had less serious perinatal complications with a significantly reduced occurrence of the composite outcome of perinatal death, shoulder dystocia, bone fracture, or nerve palsy (1% v.s. 4%, p= 0.01). However, patients in the intervention group also had higher rates of induced labour (39% v.s. 29%, p<0.001) and similar rates of CS (31% v.s. 32%, p= 0.73), and their infants were also more likely to be admitted into NICU (71% v.s. 61%, p=0.01) (260). Later, Landon and colleagues conducted another randomized clinical trial to compare the outcomes of patients with mild GDM who received routine prenatal care unaware
of the diagnosis (control group) with women who had dietary intervention, self-monitoring of blood glucose, and insulin therapy (treatment group). They demonstrated that patients in the treatment group had reduced rates of pregnancy-induced hypertension (8.6% v.s. 13.6%, p= 0.01) and a lower rate of CS (26.9% v.s. 33.8%, p= 0.02). The babies of mothers in the treatment group had lower mean birth weight (3302± 502g v.s. 3408± 589g, p<0.001), reduced fat mass (427± 198g v.s. 464±222g, p=0.003), lower risk of being LGA (7.1% v.s. 14.3%, p<0.001) and lower risk of being born macrosomic (5.9% v.s. 14.3%, p<0.001). However, the frequency of the composite adverse outcome that included stillbirth, neonatal death, hyperbilirubinaemia, hypoglycaemia, hyperinsulinaemia and birth trauma was comparable between the two groups (32.4% v.s. 37.0%,p=0.14) (351). In a recent systematic review, Hartling and colleagues concluded that treating gestational diabetes results in a lower incidence of preeclampsia, shoulder dystocia and macrosomia. However, there was still insufficient evidence to prove that treating GDM would reduce the risk of neonatal hypoglycaemia or future adverse metabolic outcomes. The only short-term harm regarding GDM treatment that was found was an increased demand for service (352).

1.6.2 Self-glucose monitoring

GDM patients can be made aware of whether the target glucose levels are being achieved or not, through self-measurement of blood glucose. Hawkins and collaborators compared the outcomes in diet-treated GDM patients who used personal glucose monitors, with those who underwent intermittent fasting glucose evaluation
during semi-weekly obstetrical visits. They found that patients in the self-BGL monitoring group had significantly fewer macrosomic and LGA infants, and also gained less weight (353, 354). These findings support the practice of self-monitoring of BGL for women with diet-treated gestational diabetes.

DeVeciana and colleagues performed a randomized clinical trial to compare the outcomes between insulin-treated GDM patients who checked for pre-prandial BGL with those who were doing 1-hour post-prandial BGL monitoring. They showed that patients using post-prandial BGL measurements had greater HbA1c change (-3.0 ±2.2 percent v.s. -0.6±1.6 percent, p<0.001); their infants had lower birth weight (3469±668g v.s. 3848±434 g, p=0.01), a lower rate of neonatal hypoglycaemia (3% v.s. 21%, p=0.05), less risk of being LGA (12% v.s. 36%,p=0.04) and were less frequently delivered by CS due to cephalopelvic disproportion (12% v.s. 36%,p=0.04) (355). This study confirmed that postprandial glucose levels are more important in terms of predicting neonatal adverse outcomes. Based on these findings, a self-monitored BGL regimen including four daily glucose checks, performed after fasting and either 1 or 2 hours after each meal was recommended (356). Weisz and collaborators conducted a prospective observational study and found that GDM patients using one hour postprandial glucose measurements had a lower need for insulin therapy (28% v.s. 40%, p<0.05) compared to patients using two hour postprandial glucose measurements. Furthermore, even though it was not statistically different, patients using one hour glucose measurements had fewer macrosomic infants (7.5% v.s. 10.6%), fewer LGA infants (7.4% v.s. 15.2%) and a lower rate of CS (24% v.s. 30%) (357).
Studies have shown that continuous glucose monitoring could even more accurately detect high postprandial blood glucose levels and nocturnal hypoglycaemic events, compared to self-monitoring of blood glucose in women with GDM (358). However, there is no established evidence regarding the cost-effectiveness of continuous glucose monitoring in GDM treatment.

1.6.3 Target blood glucose levels

Glucose control during diabetic pregnancy is a balancing act between hyperglycaemia and hypoglycaemia. Hyperglycaemia leads to LGA babies, but overly strict control of maternal glucose levels may initiate frequent maternal hypoglycaemic episodes and/or cause SGA babies. The available evidence suggests that mean plasma glucose levels around 5.8 mmol should avoid both of these adverse pregnancy outcomes (359).

The optimal therapeutic target levels remain uncertain, due to the lack of randomized trials. There is substantial inconsistency regarding the target glucose levels in different international guidelines. The most popular target glucose levels are those endorsed by ADA, ACOG, Endocrine Society and ADIPS, which stipulates: fasting glucose level ≤ 5.3 mmol/l, 1-h postprandial glucose level ≤ 7.8 mmol/l, and 2-h postprandial glucose level ≤ 6.7 mmol/l (80, 356, 360, 361). These postprandial glucose levels were supported by Veciana and colleagues; they found that achieving these target postprandial glucose levels could reduce the risk of neonatal hypoglycaemia, macrosomia, and CS (355). Similarly, the fasting glucose target is supported by Landon.
and collaborators. They found that by using this fasting glucose level as the target glucose level, patients had fewer adverse perinatal outcomes (261).

However, a recent review that included 255 pregnant women with normal weight and glucose tolerance from 12 studies, spread over half a century, reported that the weighted average glucose values (± 1 SD) were as follows: a fasting glucose level of 3.9± 0.4 mmol/l, 1-h postprandial equal to 6.0± 0.7 mmol/l, and 2-h postprandial equal to 5.5± 0.6 mmol/l. Based on these results, authors proposed that the target glucose level for GDM patients should be 4.5 mmol/l for the fasting level, 6.8 mmol/l for 1-h postprandial, and 6.1 mmol/l for 2-h postprandial, which is considerably lower than the current target glucose levels (362). Similarly, another comprehensive meta-analysis that aimed to evaluate the ideal glucose targets for GDM patients recommended a lower fasting glucose level for GDM treatment. This meta-analysis included 34 studies, enrolled 9433 women, and demonstrated that a fasting glucose target of < 5.0 mmol/l was most strongly associated with reduced risk of macrosomia (OR 0.53 95% 0.31-0.90) for GDM patients during the third trimester. However, the overall evidence is still relatively sparse, and is inconclusive in terms of selecting pre-prandial and postprandial targets for GDM treatment (363). A large, prospective randomized trial is needed to decide the optimal glucose targets for GDM patients.

1.6.4 Medical nutrition therapy (MNT)

MNT is the corner stone of GDM management. The ultimate goals of MNT are to allow appropriate weight gain based on the mother’s pre-pregnancy and prenatal weight, along with normoglycaemia, adequate fetal growth and absence of urine
ketones. An individualized nutritional counselling based on the pre-gestational BMI was recommended by the ADA (364).

There is no definitive evidence that the optimal weight gain for women with gestational diabetes is different from that of healthy women; the same recommendations for weight gain during normal pregnancy from the Institute of Medicine have been endorsed for GDM patients by a number of guidelines. Additionally, the ADA discourages weight reduction during pregnancy, in order to avoid ketosis (365, 366) (See Table 3).

Table 3 -2009 Institute of Medicine Recommendations for Total Weight Gain and Rate of Weight Gain during Pregnancy, by Pre-pregnancy BMI.

<table>
<thead>
<tr>
<th>Pre-pregnancy BMI</th>
<th>Total Weight Gain (kg)</th>
<th>Rates of Weight Gain in Second and Third Trimester (kg/week)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight (&lt;18.5 kg/m²)</td>
<td>12.5-18</td>
<td>0.51 (0.44-0.58)</td>
</tr>
<tr>
<td>Normal Weight (18.5-24.9 kg/m²)</td>
<td>11.5-16</td>
<td>0.42 (0.35-0.50)</td>
</tr>
<tr>
<td>Overweight (25.0-29.9 kg/m²)</td>
<td>7-11.5</td>
<td>0.28 (0.23-0.33)</td>
</tr>
<tr>
<td>Obese (≥ 30.0 kg/m²)</td>
<td>5-9</td>
<td>0.22 (0.17-0.27)</td>
</tr>
</tbody>
</table>

BMI, Body mass index
Nutritional recommendations generally include a carbohydrate-controlled diet that is sufficient to maintain normoglycaemia and avoid ketosis. Calorie restriction is not warranted for underweight or normal-weight GDM patients, as long as fetal growth and weight gain targets are met. Overly strict calorie restriction might increase ketosis (367) and limited studies have indicated that ketonuria may be associated with impaired psychomotor development in the offspring (368, 369). However, the ADA suggested that obese women (BMI > 30kg/m²) might benefit from a 30 percent caloric restriction (approximately 25 kcal/kg/d), and still achieve the appropriate weight gain without ketosis and intrauterine growth retardation (370).

The composition of the calories to be consumed is also a controversial topic. Jovanovic-Peterson and colleagues indicated that a low carbohydrate diet prescription, including 40% carbohydrate, 20% protein, and 40% fat that was calculated based on body weight was associated with a reduction in macrosomia incidence (371). It was reported that a low carbohydrate diet could decrease the need for insulin therapy, the incidence of having LGA infants and the rate of CS due to cephalopelvic disproportion (372). However, Moreno-Castilla and collaborators performed a randomized trial that assigned 152 GDM patients to either a 40 percent or 50 percent daily carbohydrate diet and found no difference in pregnancy outcomes (373). Moreover, Roman and colleagues found that a higher carbohydrate intake was associated with a decreased incidence of newborn macrosomia in GDM patients (374). Despite the inconsistencies in the literature, some authorities still recommend a low carbohydrate diet; carbohydrate
intake is limited to 35% -45%, and distributed in three small to moderately-sized meals, and two to four snacks (20, 375).

Carbohydrate-rich foods with a low glycaemic index (GI) appear to be healthier. In a crossover study, researchers recruited 14 non-pregnant women without diabetes, to compare the post-prandial blood glucose levels after a 540 kcal meal containing foods from a low GI group and a high GI group. Each meal contained 17% protein, 28% fat and 55% carbohydrate, but were different in the GI value (54 v. s. 92). They indicated that women in the low GI group had a significantly lower average increase in blood sugar (p<0.001) and lower insulin response (p<0.001) (376). Similarly, a small crossover study including 5 GDM patients, which aimed to compare the outcomes of a low-fat, high-carbohydrate (unrefined) diet (70% carbohydrate, 10% fat, 20% protein, and 70g fibre each day) with a low-carbohydrate and high-fat diet (35% carbohydrate, 45% fat, 20% protein, 70g fibre each day). The authors showed that patients who had the low-fat, high unrefined carbohydrate diet, had significant lower urinary glucose output (1.3± 1.1 mmol/l v.s. 2.6±3.0 mmol/l, p<0.05), lower fasting plasma cholesterol concentration (5.9±1.1 mmol/l v.s. 6.3 ± 1.1 mmol/l, p<0.01) and lower fasting free fatty acid level (590±270 µmol/l v.s. 690± 270 µmol/l, p<0.02) (377). Moreover, Moses and collaborators demonstrated that GDM patients who consumed a low GI diet required less insulin compared to those who had a high GI diet. They also found that 9 patients in the high GI group who needed insulin treatment could cease insulin use after switching to a low GI diet (378).
Maternal lipids including serum triglycerides (TGs), cholesterol, free fatty acids (FFAs) were shown to be strong predictors for fetal lipids and fetal growth in GDM patients, independent of glycaemic control (379). However, no organization currently recommends specific amounts and sources of fat consumption for GDM patients. Research indicated that mono-unsaturated fatty acids may be protective for patients with impaired glucose tolerance, whereas saturated fatty acid can increase glucose and insulin levels in women with GDM (380). A recent systematic review regarding strategies in the nutritional management of GDM patients demonstrated that a diet rich in *ad libitum* complex carbohydrates (using higher fibre and lower glycaemic index carbohydrates) and limited saturated fats might be optimal in normalizing glycaemia, preventing further insulin resistance and reducing excess fetal fat accretion. However, the evidence is far from conclusive; larger prospective and randomized trials are undoubtedly in need to identify optimal diets for GDM women (381). However, research has shown that insulin was necessary to reduce excess birth weight in the offspring of obese women with gestational diabetes, regardless of whether the appropriate glucose control was achieved (382).

1.6.5 Exercise (physical activity)

Up to 39% of women with GDM could not meet the target BGL only by diet treatment (383). Thus, physical activity, as a supplement to diet treatment, has been advocated since it can improve insulin sensitivity through increased muscle glucose uptake and glycogen synthesis (385, 386).
There is insufficient evidence to determine the most appropriate exercise regimen for GDM patients. Jovanovic-Peterson and colleagues indicated that a program that combined diet treatment and exercise was more likely to achieve normoglycaemia, and was also safe for the mother and her baby (384). Dye et al conducted a population-based study in America and demonstrated that exercise was associated with reduced rates of GDM, specifically among women with a BMI greater than 33 kg/m² (OR 1.9, 95%CI 1.2-3.1) (385). Bung and colleagues performed a prospective randomized trial to evaluate the effectiveness and safety of exercise treatment among GDM women who require insulin treatment. Patients in the exercise group had a compliance rate higher than 90%. They found that in the absence of ominous fetal heart rate (FHR) changes or significant changes in uterine activity following the exercise sessions, regular physical activity seemed to be a safe therapeutic option for GDM patients (386). Brankston et al demonstrated that compared to a diet-alone group, overweight GDM patients (BMI >25 kg/m²) in a diet-plus-exercise treatment group had lower rates of insulin use and a longer delay from GDM diagnosis to the initiation of insulin therapy (387). Based on these findings, in 2003, ACOG recommended 30 or more minutes of moderate exercise a day on most, if not all days of the week, for GDM patients without medical or obstetric complications (375, 388).

However, there were also studies that demonstrated contradictory results. Stafne and colleagues indicated that there were no differences in insulin resistance and GDM prevalence, between pregnant women who followed a 12-week standard exercise program, and pregnant women who received standard antenatal care. Furthermore,
only 55% of women in the exercise group managed to follow the recommended exercise protocol. However, these participants had a relatively low average BMI, equal to 24.8±3.2 kg/m^2, which might explain the inconsistency between different studies (389).

1.6.6 Insulin treatment

Insulin treatment is considered standard therapy in women with GDM, when target glucose levels cannot be consistently achieved through nutrition treatment and exercise. GDM patients produce insulin endogenously, but cannot meet the increased insulin requirement to counter the diabetogenic placental hormones, to maintain euglycaemia. A variety of rapid and longer acting exogenous insulin preparations are available to supplement the mothers endogenous insulin, so as to reproduce the physiological insulin requirements as close as possible in order to accomplish tight glycaemic control (390).

There is no consensus on the glucose levels that signals a necessity for insulin treatment. ACOG recommended that insulin should be administrated when fasting glucose levels are at 5.3 mmol/l or more, or if 1-h postprandial glucose levels exceed 7.2-7.8 mmol/l, or if 2-hour postprandial glucose levels reach or exceed 6.7 mmol/l (391). In Australia, prior to recent changes in guidelines (80), insulin replacement was indicated if blood glucose targets (a fasting glucose level < 5.5 mmol/l and 2-h postprandial glucose level < 7.0 mmol/l) were exceeded on two or more occasions within a 1 to 2 week interval, particularly in association with suspicion of macrosomia (392). In England, NICE recommends initiating insulin treatment after 1-2 weeks, if
lifestyle treatments are insufficient, or if fetal abdominal circumference measurements are above the 70th centile at the time of GDM diagnosis (393).

Insulin treatment could be a combination of intermediate- or long-acting and short-and rapid-acting insulin and dose adjustments are based on glucose levels at particular times of the day. Regular human insulin and neutral protamine Hagedorn (NPH) were the commonly used insulin types. Regular human insulin has been used to control the postprandial glucose level. It firstly self-collaborates to form hexamers, and then dis-collaborates into the monomeric form that can be absorbed through the capillary wall after subcutaneous injection. The slow diffusion into circulation leads to a delayed peak action as well as a longer duration of action compared to endogenous insulin, which may result in increased risk of post-meal hyperglycaemia and pre-prandial hypoglycaemia. NPH is an intermediate-acting insulin, which is used to mimic basal insulin secretion. There are also some limitations regarding NPH. The effective duration of NPH is about 16-18 h, and thus a single dose is unable to provide basal insulin for a full day. Furthermore, night-time injections of NPH may result an un-physiological rise in insulin levels in the early morning and increases the risk of hypoglycaemia (394). Rapid-acting insulin analogues such as insulin Aspart and insulin Lispro, with less time to reach peak action, have been approved by the Food and Drug Administration for use during pregnancy. Studies demonstrated comparable if not better treatment capacity and safety between rapid-acting insulin analogues and regular human insulin (395, 396). Long-acting insulin analogues including Glargine and Detemir, are also promising (397, 398). However, a large prospective clinical trial for Glargine has not been performed.
A combination of intermediate- and short-acting insulin analogues is mostly used to achieve ideal glucose control. Insulin could be administered according to the patient’s pattern of glucose concentration during the day; if the fasting glucose is elevated, evening NPH insulin injections can be used. If postprandial glucose levels are elevated, regular human insulin or rapid-acting insulin analogues can be prescribed. If both pre and postprandial glucose levels are elevated, a regimen of four injections, including 3 pre-meal short-acting insulin injections and one night NPH insulin injection could be implemented (399). Although the basal-bolus regimen more closely mimics physiological insulin secretion, the regimen itself is complicated and difficult to follow. Research has shown that there is an inverse relationship between patient compliance with treatment and regimen complexity (400). Premixed insulin formulations are produced by including a rapid-acting insulin analogue for prandial coverage and its protaminated counterpart for basal coverage, in formulations that are available in different ratios (30/70, 25/75 and 50/50). These premixed formulations can reduce the number of insulin injections to twice a day. However, an open label, randomized trial which compared the level of glycaemic control and perinatal outcomes between diabetic patients (the majority of which are GDM patients) who received insulin four times daily (3 injections after meals and 1 injection before bed) with those who received insulin twice daily (1 injection before breakfast and 1 injection before dinner), shows that GDM patients who received the four-times-daily regimen had better glycaemic control and lower rates of overall neonatal morbidity than patients who received the twice-daily regimen (401).
1.6.7 Oral hypoglycaemic agents

Traditionally, insulin therapy has been the gold standard for GDM treatment if lifestyle treatments were not enough, because a tight level of glucose control could be achieved without pharmacological treatment crossing the placental barrier. However, insulin therapy is also expensive and invasive. Oral hypoglycaemic agents are less invasive, and usually are a cheaper alternative. Oral hypoglycaemic agents also enhance the patients’ compliance to GDM treatment, while achieving similar perinatal outcomes (353).

Metformin has its major effect on lowering blood glucose by reducing hepatic glucose production. It is also able to slow intestinal glucose absorption and may have some additional effect to decrease peripheral insulin resistance (402, 403). However, Metformin crosses the placental barrier such that the fetal concentration is at least half the maternal level. However, in animal studies, using rats and rabbits, metformin is shown to not be teratogenic at doses of up to 600 mg/kg a day, which is equivalent to 2-6 times higher than the maximum recommended human dose (404). The Metformin in Gestational Diabetes (MiG) study was designed to evaluate the effectiveness and safety of metformin in the treatment of gestational diabetes. It randomly allocated 751 GDM patients to open-label treatment with metformin (1000-2000 mg daily) and insulin treatment. There was no significant difference in the primary outcomes, which is a composite of neonatal complications including hypoglycaemia, respiratory distress, hyperbilirubinaemia needing phototherapy, birth trauma, low Apgar score and
prematurity. When these adverse outcomes were compared separately, the metformin-treated group had a lower rate of hypoglycaemia but a higher number of preterm births. In the secondary outcomes, only maternal weight gain and treatment satisfaction were in favour of metformin. In the metformin group, 168 (46.3%) patients required insulin to achieve the ideal glucose level, but the median insulin dose required was lower than patients who were treated with insulin therapy only (405). Because of concerns that metformin crosses the placental barrier and may affect the babies’ metabolic function, the Offspring Follow-Up (TOFU) study was performed. This study aimed to compare the fat distribution of children born to women who participated in the MiG trial, at an age of 2 years old. The results demonstrated that the body fat percentage is comparable between the children of metformin-treated women and the children of insulin-treated women. Interestingly, children born to metformin-treated mothers had more fat being stored in subcutaneous sites. The authors suggested that a further follow-up is required to determine whether children exposed to metformin in the uterus will develop less visceral fat, or show any changes in insulin sensitivity (406).

Glyburide (glibeclamide in Australia) is a second-generation sulfonylurea drug that lowers glucose levels by increasing insulin secretion. In vitro placental perfusion studies indicated that glyburide does not cross the placenta in significant amounts (407). In 2005, Langer and colleagues reported that glyburide concentrations in neonatal umbilical cord serum at the time of delivery were below the limit of assay detection (10ng/ml) (408). However, in 2009, Hebert and collaborators found that glyburide
concentrations in umbilical cord plasma were approximately 70% of the maternal plasma concentration, by using a more sensitive assay (409).

Glyburide treatment might have comparable effects on maternal glucose control compared to insulin treatment. In a large clinical study, 404 GDM patients were randomly assigned to receive either insulin or glyburide treatment. The results indicated that there was no difference in the mean blood glucose measurement and HbA1c level. However, 18% of glyburide treated patients could not achieve the target glucose control, compared to 12% in the insulin-treated group, but patients in the glyburide group also had a significantly lower number of hypoglycaemia episodes (4% v.s. 20%, p= 0.03). The rates of preeclampsia and CS were comparable between the two groups (408). In addition, researchers demonstrated that glyburide treated GDM patients had less post-diagnosis weight gain compared to the insulin treated women (410).

Whether glyburide-treated GDM patients have comparable neonatal outcomes compared to insulin-treated patients is still controversial. London et al reported that babies born to glyburide-treated women had similar rates of LGA, macrosomia, hypoglycaemia, lung complications and NICU admission (408). Conversely, other studies reported an increased risk of neonatal hypoglycaemia, macrosomia, and NICU admission in infants of GDM patients who were treated with glyburide (411-413). A recent meta-analysis was performed to evaluate glyburide management in comparison with insulin. The authors indicated that glyburide is as effective and as well-tolerated as insulin. However, the risk of neonatal hypoglycaemia, high fetal birth weight
and macrosomia was higher in the babies born to glyburide treated women. They also suggested that a large, long term follow-up study is needed (414).

Like metformin, not all patients who received glyburide treatment achieved target glucose levels. Chmait and colleagues conducted a prospective observational study and reported a 19% failure rate in glyburide treated patients. The researchers also demonstrated that gestational age at the time of dietary treatment failure, and the mean fasting blood glucose level prior to initiating glyburide were the two most significant indicators of glyburide success (415). Based on these findings, the Endocrine Society recommended that glyburide could be used as an alternative to insulin therapy, in GDM patients who failed to achieve the target glucose level after one week of diet and exercise, except for those women who were diagnosed with GDM before 25 weeks gestation and had fasting plasma glucose levels > 6.1mmol/l (20).

1.6.8 Obstetric issues regarding GDM treatment

Obstetric surveillance is a key part in the treatment of GDM patients, and includes regular cardiotocography (CTG), ultrasound (the measurements of amniotic fluid volume, biophysical profile, and umbilical artery Doppler) and fetal movement counts. If the results of these tests are not reassuring, more aggressive options may be taken, such as a contraction stress test (OCT) or membrane rupture. There is no consensus regarding the value or timing of antepartum fetal testing. The ACOG recommends fetal surveillance in women with GDM, who display poor glycaemic control (375).
In spite of monitoring fetal vitality, ultrasound is useful for assessing fetal growth, and to provide information vital to the treatment plan. Kjos and collaborators have shown that adjusting the insulin level based on a combination of glucose testing results and fetal growth ultrasound, could identify pregnancies at low risk, and reduce the rate of CS, compared to glucose testing alone (416). Furthermore, ultrasound is also used for detection of fetal anomalies.

The timing and method of deliveries for GDM patients is an important obstetric decision. Whether elective induction reduces the risk of shoulder dystocia compared to spontaneous labour remains controversial. Kjos and colleagues randomly grouped 200 diabetic pregnant women requiring insulin (187 of whom had GDM) at 38 week of gestation into two groups, a group which had active induction of labour within 5 days, and a group which had expectant management. They found that expectant management increased the gestational age at delivery by 1 week. Patients in the expectant management group had similar rates of CS (31% v.s. 25%), but had an increased risk of LGA (23% v.s. 10%) and shoulder dystocia (3% v.s. 0%). Based on these results, the authors recommended that induced delivery should be considered at 38 weeks for women with insulin-requiring diabetes during pregnancy. However, this is the only randomized controlled trial that compared perinatal outcomes between elective induction and expectant management of labour. In a systematic review, including other retrospective information, Witkop and collaborators demonstrated that GDM patients who went through elective labour induction at term had a reduced rate of having macrosomic babies and related complications. However, they also concluded that there
was insufficient evidence to recommend induction of labour in GDM patients at 38 weeks (417).

It is also not conclusive whether elective CS should be performed on GDM patients to avoid obstructed delivery. Garabedian and co-workers conducted a systematic review and indicated that as many as 588 CS deliveries in GDM patients with an estimated fetal weight ≥ 4250g would be necessary to avoid one case of permanent brachial plexus palsy (418). In a retrospective study including more than 16000 pregnant women, Ron and colleagues found that elective CS for GDM patients who had an estimated fetal weight higher than 4500g had no significant effect on the incidence of brachial plexus injury (419). However, the ACOG still suggests that CS should be considered in women with GDM whose fetuses have a sonographically estimated weight ≥ 4500g (375).

1.7 Rationale for this research

As discussed before, the perfect treatment strategy for GDM is still unknown and different institutions have their own treatment systems. In the ACT, Australia, GDM patients are categorized into two groups based on whether they can achieve the target glucose levels by diet and exercise within one week. Patients who can achieve target BGLs with lifestyle treatment only are stratified into a low-risk group and they are referred back for usual obstetric care provided by GPs and midwives without further appointment with the diabetes team. Alternatively, patients who cannot control their glucose level only by lifestyle treatment are stratified into a high-risk group and they
attend the Diabetes in Pregnancy Service Multidisciplinary Clinic (DIPS-MDC). During the appointment in the DIPS-MDC, high-risk patients are cared for by a team including endocrinologists, diabetes educators, dietitians, midwives and obstetricians; the majority of these patients require insulin treatment. More detailed information on this stratified treatment strategy for GDM patients in the ACT is provided in the research setting (Chapter two).

1.7.1 High-risk group patients may have worse perinatal outcomes

Patients in the high-risk group who are unable to maintain the target BGLs through lifestyle changes in one week are assumed to have worse glucose tolerance and, therefore, a more severe form of GDM associated with higher rates of other risk factors such as obesity and hypertension. Some will also have previously undiagnosed type 1 and type 2 diabetes.

This assumption is supported by a previous study that used a similar stratification criterion. Wong and collaborators performed a study to examine the factors of insulin initiation in GDM patients. Notably, they used the same diagnostic criteria of GDM as in this current study, and initiated insulin treatment based on whether patients could maintain the target BGL (fasting BGL $< 5.3$ mmol/l, and $2h$ BGL $< 6.8$ mmol/l) after applying lifestyle changes for one week. Furthermore, this study was conducted in NSW, Australia, which means that the ethnic composition of their population is more likely to be similar to this study compared to the studies that have been conducted in other countries. Overall, the characteristics of the patients in their
The insulin treated group are quite similar to the high-risk group patients seen in the ACT. The author indicated that, compared to the non-insulin treated patients, their insulin-treated patients had a higher BMI (29.9 ± 7.3 kg/m² vs. 26.5 ± 6.3 kg/m², p<0.001), a higher rate of having GDM history (25.9% vs. 16.7%, p=0.006), and a higher fasting glucose level in the diagnostic OGTT test (5.57 ± 1.19 mmol/l vs. 5.05 ± 0.67 mmol/l, p<0.001). Patients in the insulin-treated group were most likely to be Anglo-European (30.8% vs. 23.8%) and least likely to be South-east Asian (17.8% vs. 28.4%) (420).

Moreover, the majority of the high-risk group patients needed insulin treatment to achieve the targeted level of glucose control. And, previous studies also demonstrated that GDM patients who needed insulin treatment had worse OGTT results and higher pre-gestational BMI, and they were more likely to be Anglo-Celtic and less likely to be Asian (421, 422).

Poor OGTT results, higher pre-gestational BMI and particular ethnicity have been shown to be associated with adverse perinatal outcomes. The HAPO study confirmed that increased levels of fasting glucose, 1-hour postprandial and 2-hour postprandial results in the OGTT test were associated with birth weight above the 90th percentile, cord-blood serum C-peptide level above the 90th percentile, primary CS and clinical neonatal hypoglycaemia (83). For pre-gestational BMI, Jensen and colleagues found that after excluding glucose intolerant patients, overweight (BMI 25.0-29.9) and obese (BMI > 30) pregnant women were associated with an increased risk of having hypertensive complications, CS, induction of labour and macrosomic babies when compared to pregnant women with normal weight (BMI 18.5-24.9) (423). This
relationship has also been confirmed by other studies (426, 427, 428). Ethnicity is also a factor that contributes to the differences in perinatal outcomes. In Australia, Wong and colleagues demonstrated that compared to South-East Asians, Anglo-European GDM patients had higher rates of CS (28.8% vs. 17.9%, p<0.01), and the babies of Anglo-European mothers also had higher birth weight (3.38 ± 0.57 kg vs. 3.18± 0.50 kg, p<0.001), higher risk of macrosomia (10.8% vs. 3.9%, p<0.01), and higher risk of being LGA (12.2% vs. 3.9%, p<0.001) when treated with similar management pathways (424). Other studies also demonstrated that compared to Caucasian GDM patients, Asian women had lower rates of primary CS (aOR = 0.86, 95% CI 0.77-0.96) and lower rates of having macrosomic infants (aOR = 0.58, 95% CI 0.48-0.70) (425).

In conclusion, patients in the high-risk group might have more risk factors that lead to worse perinatal outcomes, such as poor OGTT results and higher maternal BMI.

1.7.2 Low-risk group patients may not necessarily have better outcomes

However, there may be another side to the story. Firstly, the low-risk group of patients receive a lower level of antenatal care compared to the high-risk group; they do not have follow-up sessions with the diabetes team and they do not meet obstetricians as regularly. Previous studies have indicated that lower levels of antenatal care are associated with an increased risk of adverse outcomes. Cao and collaborators conducted a study and randomly categorised GDM patients into a group that received intensive treatment (including individualized diabetes education, dietary and exercise advice, intensive BGL monitoring, frequent clinic visits) and a group that received the
standard therapeutic regimen (including group education of diet and exercise, but no individualized appointment with a dietitian and diabetes educator and no special clinic visit). The diagnostic criteria of GDM and the criteria of insulin treatment initiation was the same between both groups. The authors found that patients in the standard treatment group had higher risk of preterm birth (8.3% vs. 2.4%, p=0.033), higher neonatal birth weight (3.45 ± 0.55 kg vs. 3.26 ± 0.53 kg, p<0.001) and higher NICU admission rates (33.3% vs. 21.3%, p= 0.036). Because the rate of insulin use between the two groups was comparable, the authors concluded that these suboptimal outcomes in the standard treatment groups could be solely attributed to the lower level of obstetric care.

Secondly, insulin therapy has been shown to improve some perinatal outcomes. Coustan and colleagues conducted a small randomized trial with 61 GDM patients, to compare two treatment regimens (insulin plus diet treatment vs. diet treatment alone) in 1978. They found that patients treated with insulin had a lower risk of having heavy infants (birth weight higher than 3856g) (427). Similar results were found in later studies. Thompson and collaborators randomized 108 GDM patients into an insulin plus diet treatment group, or a group treated through diet alone, and compared the perinatal outcomes between the two groups. The authors demonstrated that the infants of insulin-treated mothers had significantly reduced mean birth weight (3170 ± 522g vs. 3584 ± 543g, p=0.002), macrosomia rate (5.9% vs. 26.5%, p= 0.048), and lower ponderal index (2.51 ± 0.39 g/cm³ vs. 2.69 ± 0.28 g/cm³, p= 0.03) (428). Buchanan and colleagues also found that the mean birth weight, the percentile of LGA
infants and neonatal skin-fold measurements were reduced in insulin-treated GDM patients when compared to the GDM patients who were treated with diet alone (429). In a systematic review, researchers concluded that a diet plus insulin treatment could reduce the risk of having macrosomic babies in GDM patients when compared to treatment with diet alone; the risk difference was -0.098 (95% CI -0.168 to -0.028) (430).

Finally, the treatment efficacy of the low-risk group patients is largely dependent on their compliance with self-management of their lifestyle. Previous studies have shown that the compliance level to lifestyle treatments is generally not satisfactory. Cypryk and collaborators analysed the compliance of GDM patients to the recommended diets, and found that the compliance rate was only about 50% (430). Ruggiero and colleagues analysed the self-reported compliance with diabetes self-management in pre-existing diabetic patients during pregnancy. They found that achieving compliance with dietary management was more difficult than achieving compliance with other management methods including insulin administration and glucose testing (431). Similarly, in GDM patients, Carolan et al reported that they considered insulin treatment as “an easy option” compared to diet treatment (305). Hui and collaborators conducted a case study to find the obstacles facing women with GDM to follow dietary advice. They found that 1) personal food preferences conflicted with dietary advice; 2) eating in different social environments where food intake is difficult to control; 3) lack of knowledge and skills in dietary management and lack of tailored dietary planning; and 4) limited time for dietary changes, were all barriers for adherence to diet treatment (432). Moreover, research demonstrated that patients treated with
diet alone may obsessively reduce carbohydrate intake to avoid the initiation of insulin treatment. The fear of insulin outweighed the concern of eating unbalanced meals (432).

In conclusion, patients in the low-risk group may not necessarily have better perinatal outcomes than the high-risk group due to the lower level of antenatal care, differences in treatment, and potentially lower compliance with lifestyle self-management.

1.8 Research hypothesis and aims

1.8.1 Research hypothesis

Based on the arguments mentioned above, the hypothesis of this research is that compared to patients in the high-risk group, who might have worse glucose tolerance and other risk factors causing adverse perinatal outcomes, patients in the low-risk group might not necessarily have better outcomes due to a lower level of antenatal care provided, different treatments and uncertainties in compliance with lifestyle self-management.

1.8.2 Research aims

Aim one: To test the accuracy of the current stratification system of GDM treatment in the ACT, Australia. By comparing demographic data, medical history, OGTT results, and other information from low-risk and high-risk patients, the accuracy of the stratification system will be determined by whether it successfully allocates patients with better OGTT results and fewer risk factors for adverse obstetric outcomes into the low-risk group.
Aim two: To access the outcome of the current management of GDM patients in the ACT, Australia, especially for low-risk group patients. The treatment strategy for the low-risk group will be considered satisfactory if (i) patients in the low-risk group have at least as good, if not better, perinatal outcomes compared to patients in the high-risk group, and (ii) the rate of perinatal adverse outcomes among both GDM treatment groups are not higher when compared to the background population in the ACT and other related studies.
CHAPTER TWO RESEARCH SETTING AND METHODOLOGY

2.1 General information about the Australian Capital Territory (ACT) area

This research includes patients who were diagnosed with gestational diabetes mellitus in the ACT and were referred to the ACT Health Diabetes Service for education and treatment from 1\textsuperscript{st} January 2010 to 30\textsuperscript{th} June 2014. The ACT Health Diabetes Service is primarily located in The Canberra Hospital with three outreach community centres, and is responsible for the care of patients with diabetes across the ACT. The total area of the ACT is 2358 \text{km}^2, including Canberra, nearby small towns, agricultural land and national parks. The ACT has a population that has increased from about 361,900 (2010) to 384,100 (2013). Its annual population growth rate is 1.8\% (433).

Within the ACT population in 2013, 28.6\% were born in countries other than Australia. The largest immigrant populations were from North-West Europe (22.4\%) followed by South-East Asia (11.9\%) and Southern and Central Asia (10.8\%). In the ACT, the majority of employed people work in professional (29.7\%), clerical/administration (19.2\%) and management (15.8\%) occupations (434).

The number of births was 5152 in 2010, 5121 in 2011, 5461 in 2012 and 5545 in 2013. The mean age of mothers and fathers in 2013 was 31.6 years and 33.8 years, respectively, being the highest of all states and territories in Australia. From the Australian Health Survey 2011-2012, almost 63\% of people living in the ACT were overweight or obese (BMI 25 \text{kg/m}^2 or more), with the female rate being 54.7\% (435).
2.2 Pregnancy related health care in ACT

There are four hospitals that provide maternity services: two are public hospitals, The Canberra Hospital and The Calvary Hospital; while the other two are private hospitals, the Calvary Private Hospital and the Calvary John James Hospital. For women who choose the public health care system during pregnancy, their maternity health care is provided by their general practitioners (GPs) and midwives, unless they are identified as high-risk patients, for example if they have a poor obstetric history, a twin pregnancy or develop complications such as preeclampsia. The high-risk pregnant women are referred to the special antenatal clinics and are seen by obstetricians and other specialists as required. For women who choose the private health care system, their care is provided primarily by private obstetricians.

Currently, there are three pathology companies in Canberra: ACT Pathology, Capital Pathology and Laverty Pathology. Patients are free to choose one company to complete their blood and other required tests. If the tests are performed at ACT Pathology, ACT health employees can assess their patients’ results through the Clinical Information System (CIS) on the ACT Government Intranet. Capital Pathology and Laverty Pathology have not incorporated their results into the CIS yet; instead, their results are posted and/or faxed to the treating clinicians.

2.3 Diagnosis of GDM in the ACT

Within the study period of this research (01/01/2010-30/06/2014), the diagnosis of GDM was done through a two-step procedure for the majority of women according to the old ADIPS guideline published in 1998 (79). Usually, for the first step,
all pregnant women without previously diagnosed diabetes, would take a screening test for GDM, called the glucose challenge test (GCT), which was performed between 26-28 weeks of gestation. The GCT in the ACT involved the measurement of the maternal plasma glucose level one hour after the consumption of a 50g glucose load by the woman in the non-fasting status. If the result was greater or equal to 7.8 mmol/l, the patient would then undergo the second step of screening which was a 75g oral glucose tolerance test (OGTT) performed after overnight fasting. The diagnostic criteria for GDM based on the OGTT results were a fasting glucose level greater or equal to 5.5 mmol/l and/or a 2h glucose level greater or equal to 8.0 mmol/l. However, an early OGTT test, without prior GCT, was advocated at any stage during pregnancy if the clinical suspicion of GDM was high, such as obesity, previous GDM history and having a previous macrosomic baby. In this scenario, if the OGTT results were negative at an early gestational stage, this test would be repeated between 26 and 30 weeks of gestation (79). By applying this diagnostic strategy, the prevalence of GDM in the ACT increased from 49.9 per 1000 people in 2010 to 59.3 per 1000 people in 2011 (263, 441).

GDM screening could be ordered by GPs, midwives or obstetricians. The pathology laboratories released the GCT and OGTT on the same day of testing. For public patients, midwives checked the results and informed the patients of their results within the week of testing. The midwives (and private clinicians) refer patients with diagnosed GDM to the ACT Health Diabetes Service for education regarding GDM to be provided by diabetes educators and dietitians.
2.4 Stratified care system for GDM in the ACT

2.4.1 GDM education session (part one):

After being referred to the ACT Health Diabetes Service, GDM patients receive a comprehensive two-part education session provided by a registered diabetes educator and a dietitian. This education session is performed in groups of 4-8 patients. In the first part, presented by the registered diabetes educator, they are provided with information about GDM including causes, potential complications and treatment options. Additionally, they are taught how to monitor their own blood glucose levels at home. They are asked to monitor blood glucose four times a day: fasting and 2h after each of the three main meals. They are also taught to carefully record all the blood glucose values in a glucose diary provided by the educators. During this session, the women with GDM also complete two forms, the first providing key baseline demographic and pregnancy data to the clinical team (GDM Pathway Form), the other is a form that registers the GDM diagnosis with the National Diabetes Services Scheme (NDSS), which allows women to access subsidised glucose monitoring strips. The most recommended glucose meter for GDM pregnancy in the ACT is the ACCU-CHEK Performa and ACCU-CHEK Performa Nano produced by Roche (Basel, Switzerland).

Before 2013, the target blood glucose levels for GDM patients were fasting <5.5 mmol/l and 2-h < 7.0 mmol/l. After June 2013, the target blood glucose levels used by the ACT Health Diabetes in Pregnancy Service (ACTH-DIPS) were changed to fasting <5.3 mmol/l and 2h < 6.8 mmol/l after consideration of the suggested tighter targets of the Australasian Diabetes In Pregnancy Society (ADIPS) and the results of two
randomised controlled trials (RCT) conducted by Crowther and colleagues (ACHOIS) (288), and Landon and collaborators (261). Those two trials showed benefits of treating GDM using target levels close to these values chosen by the ACTH-DIPS. ADIPS has suggested tighter targets for the fasting blood glucose level of <5.1 mmol/l and the 2h blood glucose level of <6.7 mmol/l, but in the consensus guideline statement commented that further research was required before these targets could be fully endorsed (80).

2.4.2 GDM education session (part two)

After a 10-minute break, the dietitians provide the second part of the education session. During this session, information and advice regarding medical nutrition therapy (MNT) is provided. A wide range of topics are covered, for example the appropriate pregnancy rate of weight gain, food safety, adequate intake of macro- and micronutrients, and carbohydrate (CHO) counting. The recommended weight gain in pregnancy is based on the Institute of Medicine’s Guideline and is dependent on pre-pregnancy BMI. A weight gain of 12-18 kg is recommended if the patients’ pre-pregnancy BMI is less than 18 kg/m², gradually reducing to a 5-9 kg weight gain if the pre-pregnancy BMI is above 30 kg/m² (436). Based on the Healthy Eating Recommendation of the National Health and Medical Research Council (NHMRC) (437), patients are encouraged to take appropriate serves from five core food groups: vegetables, fruit, grain foods, lean meat and milk. Patients are taught how to count CHO in exchanges (one CHO exchange is equal to 15 grams of carbohydrate) and to spread
out their CHO intake within 3 meals and 3 snacks, about 2-4 exchanges per main meal and 1-2 exchanges per snack. Further, low Glycaemic Index (GI) foods and low fat intake are recommended for their diets. GDM patients are also advised to take enough calcium, iron, folate and iodine, from normal food or from supplementation. The consumption of caffeine should be minimal and alcohol should be avoided. Food safety (e.g. food preparation and the avoidance of raw food) is re-emphasized during the education session. Additionally, GDM patients are asked to keep a food record for reviewing purposes.

During the course of this study, an exercise physiologist started to attend some second part education sessions along with the dietician to provide advice regarding optimal exercise for achievement of glucose control. A 30-minute walk or equivalent moderate exercise every day was recommended.

2.4.3 Patient review and stratification into low and high-risk pathways:

Following the group education sessions (part 1 and 2), the GDM patients are requested to follow the lifestyle advice given as best they can and to start self-blood glucose monitoring at home to achieve the target blood glucose levels. All women with GDM (private and public health systems) are reviewed by a diettian of the ACTH-DIPS within one week of the education sessions.
2.4.3.1 GDM patients managed within the private health system

Patients who choose the private health system are reviewed by an ACTH-DIPS dietitian within one week of following the education sessions with the blood glucose record book to determine if lifestyle change alone is adequate to control their blood glucose. The women also receive individualised dietary advice in this session. The review results are communicated to the diabetes educators. If the patients can achieve ideal BGL control with diet and exercise changes only, their latest information regarding GDM treatment is sent to their obstetrician by diabetes educators and further reviews will be booked. If patients, however, are not maintaining target BGL levels, the diabetes educators will inform their private obstetricians and the obstetrician will refer these patients to a private endocrinologist for consideration for insulin treatment. They will then continue the antenatal care with the private obstetrician and endocrinologist, with assistance by the ACTH-DIPS diabetes nurse educators and dietitians, but they do not come to the ACTH-DIPS-MDC. However, these patients did not give birth in either The Canberra Hospital or The Calvary Hospital and their delivery information was not available. Thus, they were not included in this study.

2.4.3.2 GDM patients managed within the public hospital system

Patients who choose public hospital care are similarly reviewed one-to-one by an ACTH-DIPS dietitian within one week of the education sessions. They have their BGL record book reviewed and receive individualised dietary advice. Patients achieving their target BGL are referred back to their previously determined (usual) antenatal care
pathway. Patients who have more than three abnormal glucose readings that cannot easily be explained by diet are referred on to the diabetes educators. Then, the diabetes educators inform the endocrinologist about the patient’s situation and an appointment is arranged for them to attend the Diabetes in Pregnancy Clinic in The Canberra Hospital.

2.4.3.3 Low-risk group

The low-risk group in this research is comprised of patients who can control their glucose level by diet and exercise alone. For these patients, dietitians send a letter to their GPs, midwives and obstetricians describing their GDM status and the management that has been initiated. These low-risk group patients continue within their usual obstetric care pathway from this time, which mean they will not meet the diabetes team again unless they have trouble in maintaining target BGLs and are referred back.

The usual obstetric care pathway in The Canberra Hospital is shared care between GPs, midwives and obstetricians. After midwifery preadmission at 12-14 weeks, patients will meet their care providers about 8 times during their pregnancies. They will have two ultrasounds, one at 11-13 weeks for nuchal translucency checking and another morphology ultrasound at 18-20 weeks. They do not meet the obstetrician unless they have other risk factors, for example, gestational hypertension, placenta praevia or poor obstetric history. They are generally allowed to continue the pregnancies to 10 days beyond term if fetal monitoring is reassuring, and they are more likely to have spontaneous labour (79).
Some of the low-risk patients choose to deliver in the Calvary Hospital. The usual obstetric care pathway in The Calvary Hospital is almost the same as in The Canberra Hospital, except they have one scheduled appointment with the obstetrician at 36 weeks. Based on the BGL level, the obstetrician might arrange a growth scan ultrasound. However, the BGL levels are mostly self-reported. Like in The Canberra Hospital, care providers in the Calvary Hospital recommend that these patients continue their pregnancies up to 10 days beyond term at the latest, if no other risk factors are present.

All patients in this group are asked to contact the ACTH-DIPS if they later have more than 3 elevated BSL readings in any 5-day period. Some of these patients initially allocated to be low-risk will then be re-stratified into the high-risk category.

2.4.3.4 High-risk group

The high-risk group in this research are patients who cannot maintain their target BGLs by lifestyle treatment only on review by the ACTH-DIPS one week after the education session. These patients are referred to Multidisciplinary Diabetes in pregnancy Clinic (DIPS-MDC), which is attended by endocrinologists, dietitians, diabetes educators, midwives, obstetricians and social workers. Therefore, the patients be seen by several members of a multidisciplinary team at one single visit. Most of high-risk patients who attend the DIPS-MDC start insulin treatment; however, a small number of them continue diet treatment. This treatment decision is based on the judgement of the endocrinologist after evaluating the whole information available to them on the
individual GDM patient. This includes information on the patient’s overall medical and obstetric history, BGL record, diet and exercise compliance, stress, and the patient’s attitude toward treatment options. Patients who continue diet treatment attend the MDC regularly. Some do achieve the target BGL with extra dietary advice and are then referred back to usual antenatal care. Others eventually start insulin treatment if their glucose levels cannot be adequately controlled even after several extra weeks of lifestyle change. For patients who initiate insulin therapy, they attend this clinic every two to four weeks. During these visits, endocrinologists check the patients’ glucose levels and adjust their insulin dosages accordingly. The oral glucose lowering agent metformin is rarely used, and if so, is most often added as an adjunct to insulin therapy. However, metformin is occasionally used alone in patients in whom insulin therapy is not an option.

HbA1c, thyroid function, liver function, kidney function and vitamin D tests are also ordered by the endocrinologist. In terms of obstetric care, all these patients are able to meet with both obstetricians and midwives, instead of meeting with midwives alone. Further, patients who attend DIPS-MDC in the third trimester receive at least one growth scan ultrasound, most often at 36 weeks gestation. All the patients are required to count fetal movements at home. Fetal Non-stress Test (NST) is not routinely prescribed unless abnormal fetal movements or other risk factors are encountered. Patients who use insulin treatment, have suboptimal glucose control, or are suspected of having LGA babies, are more likely to end their pregnancies earlier at 38-39 weeks by induction of labour or elective CS in order to avoid macrosomia and obstructed labour.
2.4.3.5 Determination of the two different risk groups

These are the main characteristics of each risk group:

1) The decision to allocate patients to the low-risk or the high-risk group is made based on whether they attended the DIPS-MDC or not. Accordingly, patients who went to the DIPS-MDC one or more times and were then referred to the usual antenatal care pathway, remained in the high-risk group for the purposes of this study. Patients initially designated low-risk and managed in usual antenatal care, but were later referred to the DIPS-MDC for elevated BGLs, were also determined to be in the high-risk group.

2) The majority of the patients in the high-risk group start insulin treatment; however, a small proportion of them continue lifestyle treatment only. Conversely, patients in the low-risk group are all treated with diet and exercise.

3) Compared to the patients in the high-risk group, patients in the low-risk group have a lower level of antenatal surveillance. They have less antenatal clinic visits, less ultrasounds and blood tests, and are less likely to meet specialists individually (obstetricians and endocrinologists, dietitians and diabetes educators) regardless of the final treatment (Flow Chart 2).

Flow chart 2 - The public stratification system for GDM management in ACT Health Diabetes service.
Patients diagnosed with GDM (ADIPS, 1998):
1. 50g GCT  1h ≥ 7.8 mmol/l
2. 75g OGTT  FPG ≥ 5.5 mmol/l or/and 2h ≥ 8.0 mmol/l

Diabetes education sessions:
1. Provided by diabetes educators and dietitians
2. Provides information about GDM, advice regarding diet and exercise, and teaches self-monitoring of blood glucose levels

Home blood glucose monitoring:
1. During 1 week
2. Target glucose levels: Fasting < 5.5 mmol/l
   2h < 7.0 mmol/l  *

Review by dietitian after 1 week
Divide patients into two groups according to whether they can achieve the target blood glucose level by diet and exercise alone.

Low Risk Group:
Usual antenatal care, by GPs and midwives
Continue self-monitoring of blood glucose levels
Healthy diet and exercise reinforced

High Risk Group: **
Attend the Diabetes in Pregnancy Multidisciplinary Clinic in The Canberra Hospital
Most of them start insulin treatment
Higher level of antenatal care

*Target BGL changed from mid-2013 to: Fasting < 5.3 mmol/l, 2h < 6.8 mmol/l.

** Patients who were managed within both pathways (e.g. referred from the DIPS-MDC to complete pregnancy in the usual antenatal care pathway, or referred from usual antenatal care to the DIP-MDC) were determined to be in the high-risk group for the purpose of this study.
2.5 Methodology

This research is a retrospective clinical review of maternal characteristics and the pregnancy outcomes of women diagnosed with GDM who have attended the ACTH-DIPS. Maternal demographic and antenatal clinical information, as well as maternal and neonatal pregnancy outcome data were collected from the patient medical records. Then, descriptive and inferential statistical analyses were performed.

2.5.1 Ethics approval:

This research was a low-risk research project, as there was no direct contact with patients and de-identified data only has been used and reported. No consent form was needed. This research was conducted at The Canberra Hospital and the Calvary Hospital. Ethics approvals from the ethics committees of the two hospitals were granted before the start of this research. The Ethics Reference Numbers for this research are ETHLR.12.302 for The Canberra Hospital and 28-2014 for the Calvary Hospital. The official approval letters are shown in Appendix 1 and Appendix 2.

2.5.2 Subjects:

2.5.2.1 Inclusion and exclusion criteria:

The subjects of this research included patients who were diagnosed with GDM and referred to the ACT Health Diabetes Service for a GDM education session and risk stratification from 01/01/2010 to 30/06/2014. This research recruited patients who gave birth at The Canberra Hospital or the Calvary Hospital. If a patient had more than
one pregnancy during the research period, each pregnancy was counted as a different case.

Patients who were diagnosed with diabetes before pregnancy were excluded because they did not come to the GDM education session. Similarly, GDM patients who were referred to the ACTH-DIPS-MDC directly without attending the education session and did not go through the stratification process were not involved in this study. Unfortunately, the number of patients with pre-existing diabetes and patients who had GDM but did not go through the stratification procedure was not available due to the data collection strategy: only patients who attended the education session were identified.

Patients who delivered in private hospitals or hospitals outside of Canberra were excluded due to the lack of outcome information and heterogeneity of the treatment regimen. Multiple pregnancies were excluded from this research due to the added risk of complications compared to singleton pregnancies; Pregnancies that ended before the full 28 gestational weeks were also removed because GDM is usually diagnosed between 26-28 weeks. These patients would have had insufficient time to be categorized into either the low-risk or high-risk groups.

2.5.2.2 Medical record searching

GDM patients in the ACT who were referred to the ACTH-DIPS attended the GDM education session either in The Canberra Hospital or at the Gungahlin Community Health Centre and their attending records were stored in the ACT Patient Administration
System (ACTPAS) and Clinical Record Information System (CRIS) data bases, which were assessed for eligibility to the study. The GDM education session was ACTPAS coded for The Canberra Hospital as TGDMIG before Jan 2014, which was changed to CHGDGE after Jan 2014. The Gungahlin Community Health Centre sessions had the ACTPAS code GGDMIG. The records of all women who attended these sessions in the period of interest were reviewed and they were included in the study if they met the inclusion criteria and none of the exclusion criteria. Allocation to the low-risk or high-risk treatment groups for the purpose of this study was also determined by use of ACTPAS codes. The low-risk group patients were those who attended TGDMIG, CHGDGE or GGDMIG sessions alone. The DIPS-MDC at The Canberra Hospital was coded ANEND and ANTEND. So patients who attended one of the education sessions and were also coded as attending an ANEND or ANTEND clinics, were categorized to be in the high-risk group.

2.5.3 Data Collection

2.5.3.1 Electronic medical record systems:

Four electronic medical record systems have been used in this study.

1) Clinical Record Information System (CRIS):

CRIS contains the scanned copies of the patients’ original medical files, including the entire outpatient clinic and hospital admission records to The Canberra Hospital. It is maintained by the staff in the medical records department. The currently used version is 20.1.10.
2) Birthing Outcomes System (BOS)

BOS has the antenatal, perinatal and postnatal information of patients who delivered in The Canberra hospital, as well as the newborns. The midwives are responsible for updating it every time patients come to the hospital and receive obstetric care. The current used version is BOS 6.02.01.

3) ACT Pathology Clinical Integration System (CIS)

CIS provides pathology results of patients who have their tests performed by ACT Pathology to authorized clinicians. It can be accessed through the ACT Health intranet https://actpath/cis/cis.dll.

4) BirthPac

BirthPac is an obstetrics-reporting package used in the Calvary Hospital. Just like the BOS at The Canberra Hospital, it covers information of mothers, births and infants and is maintained by the midwives. The currently used version is 1.2.608.

2.5.3.2 Pathological data collection:

All the pathology data of patients who had their blood tests performed by ACT Pathology were collected from CIS by searching their Medical Record Numbers (MRNs). This information included GCT and OGTT results. For the high-risk group, outcomes of HbA1c, TSH and Vitamin D tests were also extracted. The GCT and OGTT results performed by pathology laboratories other than ACT Pathology were collected
from the medical records if they were noted by clinicians during clinic visits. Unfortunately, some GCT and OGTT results could not be found by all means available.

2.5.3.3 Maternal demographic data collection:

Maternal demographic information was collected from the ACT Health Gestational Diabetes Mellitus Clinical Pathway Form. Each newly diagnosed GDM patient is asked to complete this form, regardless of whether they planned to deliver in the ACT or not. The demographic information is based on self-report, including age, pre-pregnancy weight, height, gestation, parity, previous history of GDM, family history of diabetes, smoking status, consumption of alcohol and other medical illnesses including hypertension, hypothyroidism, hyperthyroidism, asthma, polycystic ovary syndrome (PCOS). The gestational week when a patient completed this form was used as the GDM diagnosed time. The gestational week was calculated based on the date of the last normal menstrual period often confirmed by an early week ultrasound, or by a dating ultrasound if the menstrual history was unreliable.

Gestational week at first appointment and country of birth were collected from either the BOS Antenatal Assessment section if delivered at The Canberra Hospital or the Event Summary Form from the BirthPac system if delivered at the Calvary Hospital. Due to the nature of self-reporting, this part of the data is less reliable.
2.5.3.4 Outcome information collection at The Canberra Hospital

1) Maternal complications:

The diagnoses of maternal complications that related to GDM were collected from the Maternal Admission Summary Form in CRIS and the Antenatal Summary in BOS. In order to achieve the greatest accuracy, all the notes of ANEND and ANTEND clinics were reviewed. Maternal complications were also recorded if noted by the doctors during the clinic visits.

These complications included gestational hypertension (GH), preeclampsia (PE). The diagnostic criteria of these complications at The Canberra Hospital were the same as outlined in the latest guideline from The Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG). GH was defined as new onset of hypertension (≥ 140 mmHg systolic or ≥ 90 mmHg diastolic) after 20 weeks gestation. PE was classified as newly developed hypertension after 20 weeks gestations combined with existence of at least one of the following new-onset conditions, including proteinuria (spot urine protein/creatinine ≥30 mg/mmol or ≥ 300 mg urinary protein/day or at least 1 g/L on urine dipstick testing), other maternal organ dysfunction and uteroplacental dysfunction (438).

2) Delivery information:

The intrapartum information was collected from the neonatal sections of BOS, as well as Birth Summary Forms, ACT Midwives Data Collection Forms and Discharge
Summary Forms from CRIS. This information included onset of delivery (spontaneous onset, induction and no labour), mode of delivery (spontaneous labour, induced labour, elective CS and emergency CS), method of birth (normal birth, forceps, vacuum and CS), reasons for elective CS and emergency CS, perineal status including sutured status, gestational week of delivery, after delivery bleeding, length of hospitalization (after delivery), presence of the meconium and shoulder dystocia. Shoulder dystocia was defined as a vaginal cephalic delivery that requires additional obstetric manoeuvres to deliver the fetus after the head has delivered and gentle traction has failed (439).

3) Neonatal information:

Neonatal information was collected from the same documents as delivery information. It included birth status (live and stillbirth), Apgar score, gender, birth weight, birth length and admission to Neonatal Intensive Care Unit (NICU) and/or Special Care Nursery (SCN). The diagnoses of neonatal hypoglycaemia, neonatal jaundice and neonatal respiratory distress were recorded if mentioned.

Neonatal hypoglycaemia was defined as blood glucose level less than 2.6 mmol/l. The diagnoses of neonatal jaundice were based on yellow colouration of the skin and the sclera caused by a raised level of bilirubin in the circulation. Respiratory distress was defined as having grunting, flaring or retractions and/or respiratory rate outside the normal range (40-60 times per minute) (440).
4) NICU and SCN admission information

The Medical Record Numbers (MRN) of infants who were admitted into NICU and SCN were extracted from the mothers’ medical records. By searching these MRNs, a new research group, infants in NICU (SCN) was generated. The information regarding diagnoses and treatments of these neonates were collected from the Department of Neonatology Centenary Hospital Discharge Summary Forms in CRIS. Also, the reason for admission, the length of hospitalization, main diagnoses and treatments were recorded from these records.

Based on the local policy, infants with BGLs less than 1.5 mmol/l were admitted into the NICU immediately for intravenous infusion of 10% dextrose. If BGLs were in the range of 1.5-2.0 mmol/l, NICU or SCN admissions were considered for initiation of 2 hourly supplementary feeds. Jaundiced infants requiring peripheral IV fluids and closer monitoring were also admitted in to NICU/SCN. The decision between treatments with phototherapy or exchange transfusion was made based on the guideline for Serum Bilirubin (SRB) levels and outcomes of phototherapy (Appendix 3). For infants with respiratory distress, those requiring crib oxygen, up to 25% or low flow oxygen were admitted into SCN, while those who needed continuous positive airway pressure (CPAP) or high flow oxygen were nursed in the NICU. Mechanical ventilation was indicated for infants managed with CPAP treatment if one of the following situations occurred: significant respiratory distress, respiratory failure (pCO₂ > 55mmHg) or progressive hypoxaemia [despite fraction of inspired oxygen (FiO₂) up to 0.6].
2.5.3.5 Outcome information collection at the Calvary Hospital

1) Maternal Complications:

The diagnoses of maternal complications related to GDM were collected from the Antenatal Notes sections in the BirthPac system. These complications include GH and PE.

Based on the local policy of the Calvary hospital, GH was diagnosed as hypertension arising in pregnancy after 20 weeks gestation without any other feature of a multi-system disorder. The diagnostic criteria for preeclampsia were: hypertension arising after 20 weeks gestation and the new onset of one or more of the following situations: proteinuria, renal insufficiency, liver disease, neurological disturbances or haematological disturbances.

2) Delivery information

The Event Summary Form and the Discharge Summary Form in the BirthPac system provided the delivery details. This information included onset of delivery (spontaneous onset, induction and no labour), mode of delivery (spontaneous labour, induced labour, elective CS and emergency CS), method of birth (normal birth, forceps, vacuum and CS), reasons for elective CS and emergency CS, perineal status including sutured status, gestational week of delivery, after delivery bleeding, length of hospitalization (after delivery), presence of meconium and shoulder dystocia.
3) Neonatal information

The Mother’s Infant section in the BirthPac system provides general information about the newborn. Data regarding birth status (live and stillbirth), Apgar score, gender, birth weight, birth length, admission to NICU and/or SCN, neonatal morbidities and treatments were collected. However, the detailed medical records of neonates admitted into the NICU or SCN were not available in the BirthPac system.

Based on the local policies of the Calvary hospital, neonatal hypoglycaemia was diagnosed as a blood glucose level of 2.5 mmol/l or below. The neonates were admitted to SCN if their BGL was less than 2 mmol/l. Intravenous treatment with 10% Dextrose was indicated for BGLs of <1.6 mmol/l. Neonatal jaundice was diagnosed based on yellow discoloration of infants’ skin and sclera, caused by increased bilirubin level. Jaundiced infants requiring peripheral IV fluid therapy and closer monitoring were sent to the SCN. Treatment for jaundice was based on the SRB and was recorded in Neonatal Phototherapy Record charts. Respiratory distress was defined as having grunting, flaring or retractions and/or respiratory rate outside the normal range (40-60 times per minute). The infants requiring oxygen therapy were admitted to the SCN. Severe cases were transferred to the NICU at The Canberra Hospital (See table 4).
Table 4 - Data collection from the medical record system

<table>
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<tr>
<th>Maternal demographic data</th>
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<th>For patients in the Calvary Hospital</th>
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Maternal Pathology Data

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Maternal Outcomes Information

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**Neonatal Outcome Information**

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<th>Diagnosis neonatal complications</th>
<th>Birth Summary Form</th>
<th>Mother’s infants</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACT Midwives Data Collection Form</td>
<td>ACT Midwives Data Collection Form</td>
<td>in BirthPac</td>
</tr>
<tr>
<td>Discharge Form in CRIS/Neonatal section in BOS</td>
<td>Discharge Form in CRIS/Neonatal section in BOS</td>
<td></td>
</tr>
<tr>
<td>ACT Midwives Data Collection Form Discharge Form in CRIS/ Neonatal section in BOS</td>
<td>NICU/SCN Admission Information</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td><strong>reasons for admission</strong></td>
<td>Department of Neonatology Centenary Hospital Discharge Summary Form in CRIS</td>
<td>Nil</td>
</tr>
<tr>
<td><strong>length of stay in NICU/SCN</strong></td>
<td>Department of Neonatology Centenary Hospital Discharge Summary Form in CRIS</td>
<td>Nil</td>
</tr>
<tr>
<td><strong>main diagnosis and treatment</strong></td>
<td>Department of Neonatology Centenary Hospital Discharge Summary Form in CRIS</td>
<td>Nil</td>
</tr>
</tbody>
</table>

GDM, gestational diabetes mellitus; GCT, glucose challenge test OGTT oral glucose tolerance test;
GH, gestational hypertension; PE, preeclampsia; NICU, neonatal intensive care unit; SCN, special care nurseries;
CRIS, clinical record information system; BOS, birthing outcomes system; CIS, ACT pathology clinical integration system

2.5.4 Data management

2.5.4.1 Data security:

Microsoft Office Excel 2007 was used to store and process data in this study. All data was stored in a password protected Excel file. Patients’ MRNs and the assigned case numbers were recorded in a lab notebook manually and locked in an assigned bookcase located in the office of the Department of Endocrinology and the ACT Diabetes Service in The Canberra Hospital (Building 6, Level 3).
2.5.4.2 Data settlement:

For analysis purposes, the original data was managed as follows. BMI was calculated using the formula $\text{BMI} = \text{bodyweight (kg)} / \text{height}^2 \text{ (m}^2\text{)}$. Based on the countries of birth, patients were divided into the following ethnic groups: Anglo-European (Australian, New Zealander, American and European), South Asian (Indian, Pakistani, Sri Lankan, Nepalese, Bangladeshi and Bhutanese), South-East Asian (Chinese including from Hong Kong and Taiwan, Vietnamese, Thai, Cambodian, Filipino, Malaysian, Indonesian, Lao people, Burmese, Korean and Japanese), Pacific Islander (Samoa, Tongan, Papua New Guinean and Fijian), Middle-Eastern (Syrian, Iranian, Iraqi, Jordanian and Afghanistan), and others (424).

The outcome information also needed to be redefined. Preterm birth was defined as patients delivering before 37 weeks and patients who gave birth after 42 weeks were identified as post-term birth (441). Apgar scores at 5 min of age were classified into three ordinal groups: low (Apgar 0-3), intermediate (Apgar 4-6), and normal (Apgar 7-10). Low Apgar score is closely related to the occurrence of neonatal adverse outcomes (442). Macrosomia was defined as birth weight greater than or equal to 4000g (443), while low birth weight was defined when birth weight was less than 2500g, both irrespective of the gestational age (444). Small for gestational age (SGA) refers to a birth weight below the 10th percentile of the general population after adjustment for gestational age and gender (445). Alternatively, large for gestational age (LGA) was defined as birth weight above the 90th percentile after adjustment for gestational age and gender. A centile calculator was used to calculate the customized
birth weight percentage, which was specifically designed for the Australian population. Except for gestational age and neonates’ gender, customized birth weight centile also adjusted for maternal height, weight, ethnicity and parity (90, 446). Ponderal index (PI), another measurement of body size, was also calculated for the neonates. PI yields valid results even for very short and very tall persons and that is the reason why it is commonly used in paediatrics. It is a ratio of body weight to length expressed as $PI = \frac{\text{weight} \ (g) \times 100}{\text{length} \ ^3 \ (\text{cm}^3)}$. According to some authorities, normal PI value is from 2.32-2.85 g/cm$^3$. Neonates with a PI greater than 2.85 are classified as obese, while those with a PI less than 2.32 are classified as thin (447).

While the majority of the patients categorized into the high-risk group received insulin, some did not. For some data analyses, the high-risk group was separated into subgroups, those receiving insulin [high-risk insulin treated (HRI)] and those treated with diet only [high-risk diet treated (HRD)]. Patients in the HRD subgroup were mostly those referred by their midwives and GPs to the DIPS-MDC due to abnormal BGL. However, rather than starting insulin, the endocrinologists considered that there was a reasonable chance that extra attention to diet or approaches to manage stress could improve their glycaemic control. A few patients attended as HRD patients due to psychosocial issues and/or language difficulties. The HRD patients attending the DIPS-MDC were reviewed by the full team, including endocrinologist and obstetrician. Those HRD patients who achieved target BGL following one or more visits to the DIPS-MDC were referred back to the usual antenatal care pathway, unless the treating clinicians had other antenatal concerns. These patients kept stayed within the category of HRD
for the purposes of this study. Those patients initially managed with diet in the DIPS-MDC, but subsequently treated with insulin, were categorized in the HRI subgroup for the purposes of this study.

Data reliability was evaluated based on two factors: accuracy of data recording and collection, and number of missing data. Information that was clearly recorded in the electronic medical record system and percentage of missing data is lower than 10% were deemed as data with good reliability. Otherwise, the data reliability is intermediate if there is inconsistency in results from different medical record systems, or the percentage of the missing data is higher than 10%. The data reliability is classified as low when the percentage of the missing data is higher than 50%.

2.5.5 Statistical methods

2.5.5.1 Sample size calculation:

The hypothesis of this research was that outcomes in the low-risk group may not be better than in the high-risk group due to a lower level of antenatal surveillance and different treatment composition. Since birth weight is one of the primary outcomes of GDM patients, a difference of 100 g in the mean birth weight, if adjusted for gestational age, between the two research groups, either heavier or lighter, was considered clinically significant. The variation of the study population was determined from using the results of the HAPO study, which is the largest clinical data set in GDM research, with almost 25,000 participants. The standard deviation of birth weight in the HAPO study was 529g (83). By applying the equation of sample size calculation, n=
\[(Z_{\alpha/2} + Z_\beta)^2 \times 2 \times \sigma^2 / d^2\] (\(\alpha\)=confidence level, \(1-\beta\)= power, \(\sigma\)= measurement variation, \(d\)= smallest meaningful difference to be detected), it is determined that at least 439 patients are required in each group to detect a 100g difference in birth weight with a 95% confidence level and a power of 80%.

2.5.5.2 Statistical analysis

Tabulation of data and statistical analysis were performed using SPSS-version 21.0. Kolmogorov-Smirnov test was used to exam whether the continuous data follow a normal distribution. The means of the parametric variables were compared using Student’s t-test whereas non-parametric data were compared using Mann Whitney U Tests. Categorical data were analysed using Chi square \((x^2)\) tests and Fisher’s exact tests -- for contingency tables with minimum expected frequencies of less than 5. Stepwise logistic regression was performed for variables that were significant in univariate analysis to control for confounders. Odds ratios (ORs) with a 95% confidence interval (CIs) were calculated for variables of interest. Confidence intervals excluding 1.0 were considered significant. All tests were two-tailed with \(p< 0.05\) considered significant.
CHAPTER THREE RESULTS

3.1 General information:

From 01/01/2010 to 30/06/2014, 1428 patients were diagnosed with GDM and were referred to the ACT Health Diabetes Service for education sessions. Among these patients, 414 were excluded from this study because their deliveries occurred in hospitals other than The Canberra Hospital and the Calvary Hospital. Further, patients who had twin pregnancies (36 cases), triple pregnancy (1 case) and delivery before the 28th gestational week (2 cases) were also removed from the study population. Consequently, 975 patients were included in this study, with 509 in the low-risk group and 466 in the high-risk group (Flowchart 3). This number fulfilled the sample size requirement to detect a 100 g difference in birth weight, with 95% confidence level and power of 80%.
Flowchart 3 - Study Population.

1428 patients were diagnosed with GDM and attended the education session *

414 patients had no delivery information

1014 patients gave birth in either The Canberra Hospital or The Calvary Hospital

36 twins
1 triplet
2 patients delivered before 28 weeks

975 patients in the research group

509 patients in the low-risk group
466 patients in the high-risk group

* This number does not include patients who received care from the DIP pregnancy service but did not attend the GDM education session and stratification procedures (e.g. women with pre-existing diabetes or late transfers from other hospitals).
3.2 Maternal demographic information

3.2.1 Maternal age, BMI, gestational age at first appointment, gestational age at GDM diagnosis, number of gestations and parity

GDM patients in the low-risk group were younger (31.7 ± 4.8 years-old compared to 32.6 ± 5.3 years-old, p= 0.009), and had a lower BMI (26.3 ± 6.7 kg/m² v.s. 29.3 ± 7.5 kg/m², p< 0.001). Low-risk group patients also had later first appointments with their care providers (15.1 ± 6.6 gestational weeks v.s. 13.2 ± 7.3 weeks, p< 0.001), later diagnosis of GDM (28.3 ± 2.8 gestational weeks v.s. 26.6 ± 4.5 weeks, p< 0.001), and a lower percentage of patients diagnosed with GDM before 24 weeks of gestation (6.0% v.s.18.9%, p<0.001). Interestingly, of the 975 women making up this study cohort, only 47 had diabetes in pregnancy according to WHO criteria. Moreover, of these 26 were stratified to the high risk group and 21 were stratified to the low risk groups (non-significant; p=0.28). Patients within the low-risk group had fewer pregnancies (2.1 ± 1.3 times v.s. 2.5 ± 1.8 times, p<0.001), as well as fewer births (0.73 ± 1.0 times v.s. 0.98 ± 1.2 times, p< 0.001) (Table 5).
Table 5 - Maternal age, BMI, gestational age at first appointment, gestational age at GDM diagnosis, number of gestations and parity.

<table>
<thead>
<tr>
<th></th>
<th>Low-risk group (n=509)</th>
<th>High-risk group (n=466)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years-old)</td>
<td>31.7 ± 4.8</td>
<td>32.6 ± 5.3</td>
<td>0.009</td>
</tr>
<tr>
<td>BMI (kg/m^2)</td>
<td>26.3 ± 6.7</td>
<td>29.3 ± 7.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gestational age at first appointment (weeks)</td>
<td>15.1 ± 6.6</td>
<td>13.2 ± 7.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gestational age at GDM diagnosis (weeks)</td>
<td>28.3 ± 2.8</td>
<td>26.6 ± 4.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diagnosed with GDM before 24 gestational weeks (%)**</td>
<td>6.0%</td>
<td>18.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gravida (times)</td>
<td>2.1 ± 1.3</td>
<td>2.5 ± 1.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Parity (times)</td>
<td>0.73 ± 1.0</td>
<td>0.98 ± 1.2</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Student’s t-test was used.

** Chi-square test was used

Regarding data reliability, less than 10% of the cases had missing data (Table 6). However, these data are self-reported, and the reliability is intermediate.
Table 6 – Prevalence of cases with missing data on maternal age, BMI, gestational age at first appointment, gestational age at GDM diagnosis, number of gestations and parity.

<table>
<thead>
<tr>
<th></th>
<th>Number of cases with missing data (%)</th>
<th>Low-risk</th>
<th>High-risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td>0.8%</td>
<td>0</td>
</tr>
<tr>
<td>Gestational age at first appointment</td>
<td></td>
<td>0.8%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Gestational age at GDM diagnosis</td>
<td></td>
<td>1.2%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Diagnosed with GDM before 24 gestational weeks (%)</td>
<td></td>
<td>1.2%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Gravida</td>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
3.2.2 History of GDM, family history of diabetes

The prevalence of previous history of GDM and of family history of diabetes were lower in the low-risk group, compared to the high-risk group patients, 13.2% v.s. 23.2%, p< 0.001, and 55.4% v.s. 67.0%, p=0.001, respectively (Chart 2).

Chart 2 - History of GDM and family history of diabetes.

* 2*2 Chi-square ($\chi^2$) test was used.
Data reliability: less than 10% of the cases had missing data regarding history of GDM and family history of diabetes (Table 7). Based on the nature of self-report information, the reliability of these data is intermediate.

Table 7—Prevalence of cases with missing data regarding GDM history and family history of diabetes.

<table>
<thead>
<tr>
<th></th>
<th>Number of cases with missing data (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low-risk group</td>
</tr>
<tr>
<td>GDM History</td>
<td>0</td>
</tr>
<tr>
<td>Family History of Diabetes</td>
<td>0.2%</td>
</tr>
</tbody>
</table>
3.2.3 Smoking status and alcohol consumption

The two groups had comparable number of patients who continued smoking (10.1% v.s. 10.1%, p= 0.996), and consumed alcohol (5.4% v.s. 4.7%, p= 0.653) during pregnancy (Chart 3).

Chart 3 - Smoking status and alcohol consumption during pregnancy.

* 2*2 Chi-square ($\chi^2$) test was used.
Data reliability: The prevalence of cases with missing data regarding smoking status and alcohol consumption was less than 10% (Table 8). Based on the nature of self-reporting information, the reliability of these data are intermediate.

Table 8 - Missing data on smoking status and alcohol consumption.

<table>
<thead>
<tr>
<th></th>
<th>Number of cases with missing data (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low-risk group</td>
</tr>
<tr>
<td>Smoking</td>
<td>4.7%</td>
</tr>
<tr>
<td>Alcohol Consumption</td>
<td>4.7%</td>
</tr>
</tbody>
</table>
3.2.4 Maternal ethnicity

Based on the country of birth, mothers in the low-risk group were mostly Anglo-European (56.3%), followed by South-East Asian (19.4%), South Asian (18.0%), Pacific Islander (1.6%), Middle-Eastern (1.2%) and other ethnicities (3.6%). In the high-risk group, the majority of patients were Anglo-European (58.7%), followed by South Asian (21.4%), South-East Asian (11.9%), Middle-Eastern (1.7%) Pacific Islander (1.1%), and other ethnicities (5.2%). Only the proportion of South-East Asian patients was statistically different between two groups with more South-East Asians in the low-risk group (19.4% v.s. 11.9%, p=0.002) (Chart 4).

Chart 4 - Maternal Ethnicity

* 2*2 Chi-square (x²) test was used
Data reliability: There are 12 missing data in this section, 1.6% in the low-risk group and 0.9% in the high-risk group (Table 9). This ethnicity information is based on self-reporting. The patients’ ethnicity is defined by the country of birth. There might be patients who born in Australia or other countries, but from ethnic backgrounds with higher GDM risk than the general population (eg: Asian, Maori). So, the reliability is intermediate.

Table 9 - Missing data on maternal ethnicity.

<table>
<thead>
<tr>
<th>Maternal ethnicity</th>
<th>Number of cases with missing data (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-risk group</td>
<td>1.6%</td>
</tr>
<tr>
<td>High-risk group</td>
<td>0.9%</td>
</tr>
</tbody>
</table>
3.2.5 Maternal pre-existing complications

GDM patients in the low-risk group had lower prevalence of hypothyroidism (4.5% v.s. 7.7%, p=0.036) and of essential hypertension (0.6% v.s. 3.4%, p=0.001). There were no differences between low- v.s. high-risk groups regarding the prevalence of hyperthyroidism (0.6% v.s. 0.9%, p=0.619), asthma (3.7% v.s. 4.7%, p=0.443), and PCOS (2.9% v.s. 3.6%, p=0.539) (Chart 5).

Chart 5 - Maternal pre-existing complications.

* 2*2 Chi-square (x²) test was used in comparing hypothyroidism, asthma, PCOS. Fisher’s exact test was used to compare essential hypertension and hyperthyroidism.

Data reliability: There is no missing data regarding this part of information. Due to the nature of self-reporting data, the reliability is intermediate.
3.2.6 GCT and OGTT results

Patients in the low-risk group had lower 1-h glucose levels in the GCT test (8.9 ± 1.1 mmol/l v.s. 9.2 ± 1.5 mmol/l, p = 0.003) and lower glucose levels while fasting, during the OGTT (4.9 ± 0.5 mmol/l v.s. 5.0 ± 0.8 mmol/l, p < 0.001). Interestingly, both groups had similar glucose levels, both 1-h (9.6 ± 1.4 mmol/l v.s. 9.8 ± 1.4 mmol/l, p = 0.137) and 2-h (9.0 ± 1.0 mmol/l v.s. 9.0 ± 1.0, p = 0.388) at the OGTT (Table 10).

Table 10 - GCT and OGTT results.

<table>
<thead>
<tr>
<th></th>
<th>Low-risk Group</th>
<th>High-risk Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCT (mmol/l)</td>
<td>8.9 ± 1.1</td>
<td>9.2 ± 1.5</td>
<td>0.003</td>
</tr>
<tr>
<td>OGTT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting (mmol/l)</td>
<td>4.9 ± 0.5</td>
<td>5.0 ± 0.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>OGTT 1H (mmol/l)</td>
<td>9.6 ± 1.4</td>
<td>9.8 ± 1.4</td>
<td>0.137</td>
</tr>
<tr>
<td>OGTT 2H (mmol/l)</td>
<td>9.0 ± 1.0</td>
<td>9.0 ± 1.0</td>
<td>0.388</td>
</tr>
</tbody>
</table>

* Student’s t-test was used.

** GCT, Glucose Challenge Test; OGTT, Oral Glucose Tolerance Test

Data reliability: more than 10% of the cases have missing GCT and OGTT data (Table 11). These data were collected from the CIS. By considering the relatively large number of missing data, the reliability is intermediate.
Table 11 - Missing data of GCT and OGTT results.

<table>
<thead>
<tr>
<th></th>
<th>Number of cases with missing data (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low-risk group</td>
</tr>
<tr>
<td>GCT</td>
<td>29.1%</td>
</tr>
<tr>
<td>OGTT Fasting</td>
<td>10.4%</td>
</tr>
<tr>
<td>OGTT 1H</td>
<td>12.6%</td>
</tr>
<tr>
<td>OGTT 2H</td>
<td>12.6%</td>
</tr>
</tbody>
</table>

* GCT, Glucose Challenge Test; OGTT, Oral Glucose Tolerance Test
3.2.7 Summary of maternal information:

Patients in the low-risk group were younger and leaner. They had lower gravida, lower parity, and less personal history of GDM and family history of diabetes. There were more South-East Asian women in the low-risk group. Both groups had similar prevalence of smoking and alcohol consumption during pregnancy. In terms of pre-existing complications, patients in the low-risk group had lower prevalence of hypertension and hypothyroidism. Additionally, patients in the low-risk group had lower GCT and fasting glucose results of the OGTT. However, the 1-h and 2-h results of the OGTT were not statistically different between the two groups.

In conclusion, low-risk group patients had less risk factors for adverse perinatal outcomes, as well as lower GCT results and fasting glucose level of OGTT, which indicated that the stratification system for GDM in the ACT is effective at differentiating risk.
3.3 Maternal outcomes

3.3.1 Gestational hypertension (GH) and preeclampsia (PE)

Patients in the low-risk group had lower prevalence of GH (3.9% v.s. 7.7%, p=0.011). They also have lower prevalence of PE, but it was not statistically different (2.2% v.s. 4.1%, p=0.084). However, the low-risk group patients had lower overall risk of developing pregnancy-induced hypertension, which includes GH and PE (6.1% v.s. 11.8%, p= 0.002) (Chart 6).

Chart 6 - Pregnancy-induced hypertension.

* 2*2 Chi-square (x^2) test was used.

** GH, gestational hypertension; PE, preeclampsia
3.3.2 Gestational age, preterm birth and post-term birth

Patients in the low-risk group delivered later than the high-risk group patients (39.0 weeks v.s. 38.7 weeks, p < 0.001). More patients delivered after 40 weeks of gestation in the low-risk group compared to the high-risk group (33.4% v.s. 8.6%, p<0.001). Of note, one patients in the high-risk group delivered at 42 weeks, which could be diagnosed as post-term birth.

Interestingly, the prevalence of having preterm births was significantly higher in the low-risk group patients (9.8% v.s. 6.0%, p= 0.028). In the multi-variant regression model, the risk of preterm birth was still higher in the low-risk group (OR 1.897, 95%CI 1.137 – 3.164, p= 0.014), even after controlling for age (OR 1.050, 95%CI 0.998-1.106, p= 0.062), parity (OR 0.713, 0.523-0.972, p = 0.032), smoking status (OR 0.994, 95%CI 0.429-2.304, p = 0.988) and alcohol consumption (OR 1.664, 95%CI 0.661-4.187, p= 0.279).

Among the low-risk patients, 6.1% had preterm spontaneous onset of labour, while 1.0% had preterm induction of labour and 2.8% had preterm birth without labour. Alternatively, in the high-risk group patients, 2.6% had preterm spontaneous labour, 1.3% had preterm induction and 2.1% had preterm birth without labour. Low-risk patients had higher rates of spontaneous preterm labour compared to the high-risk group (6.1% v.s. 2.1%, p= 0.010), however, the rates of having induced preterm birth and preterm birth without labour were not statistically different, p value equal to 0.656 and 0.370, respectively (Chart 7).
Chart 7 - The onset of preterm birth.

* 2*2 Chi-square ($x^2$) test was used.

Data reliability: There is no missing data in this part of information. The gestational age is precisely recorded in the medical forms. The reliability of this information is good.
3.3.3 Onset of birth, mode of delivery and methods of birth

1) Onset of birth

Patients in the low-risk group had a higher rate of spontaneous-onset labour (59.9% v.s. 27.0%, p< 0.001). The rate of induced onset of labour was lower in the low-risk group (23.2% v.s. 50.6%, p< 0.001). Similarly, the rate of patients who did not undergo labour was lower in the low-risk group compared to the high-risk group (16.9% v.s. 22.3%, p= 0.033) (Chart 8).

* 2*2 Chi-square (x^2) test was used.
2) Mode of delivery

Patients in the low-risk group had a higher rate of spontaneous deliveries (spontaneous onset of labour and vaginal delivery) (52.1% v.s. 21.9%, p<0.001), but a lower rate of induced deliveries (induced onset of labour and vaginal delivery) (17.1% v.s. 38.6%, p<0.001) and a lower rate of elective CS (14.1% v.s. 20.4%, p=0.010). Interestingly, patients in the low-risk group had a similar rate of emergency CS (16.7% v.s. 19.1%, p=0.328) (Chart 9).

![Chart 9 - Mode of delivery.](image)

* 2*2 Chi-square ($x^2$) test was used.
3) Methods of birth

In the low-risk group, patients had a higher rate of normal vaginal delivery (53.8% v.s. 45.9%, p= 0.014), and a lower rate of CS (30.8% v.s. 39.7%, p= 0.004). However, the prevalence of instrumental delivery was comparable between the two groups. In the low-risk group, 8.6% of the patients needed forceps during labour, compared to 8.4% of the patients in the high-risk group (p= 0.878). Vacuum extractors were used in 6.7% of the deliveries in the low-risk group, compared to 6.0% in the high-risk group (p= 0.668) (Chart 10).

Chart 10 -Methods of birth.

* 2*2 Chi-square (x²) test was used.

Data reliability: There is no missing data in this section. All data were accurately recorded in the medical form. The reliability is good.
3.3.4 Reasons for elective CS and emergency CS

1) Reasons for elective CS

Patients in the low-risk group compared to the high-risk group delivered by elective CS had comparable indications of repeated CS (54.2% vs. 60.0%, p= 0.450), malpresentation (15.3% vs. 14.7%, p= 0.922), intrauterine growth restriction (IUGR) (1.4% vs. 1.1%, p= 0.843), and unspecified reason (19.4% vs. 16.8%, p= 0.664). However, the low-risk group patients had more elective CSs because of placenta praevia (8.3% v.s. 3.2%, p< 0.001) while there were more high-risk group patients who had elective CS because of LGA (4.2% v.s. 1.4%, p= 0.006) (Chart 11).

Chart 11 -Reasons for elective CS.
* 2*2 Chi-square ($x^2$) test was used to compare the indications of repeated CS, malpresentation, and other reasons. Fisher’s exact test was used to compare indications of placenta praevia, LGA, and IUGR.

** LGA, large for gestational age; IUGR, intrauterine growth restriction
2) Reasons for emergency CS

Among the reasons for performing emergency CS, the low-risk group had comparable rates of obstructed labour (27.4% vs. 38.2%, \( p = 0.147 \)), fetal distress (38.1% vs. 37.1%, \( p = 1.000 \)) and non-significant trends for reduced obstructed labour combined with fetal distress (7.1% vs. 15.7%, \( p = 0.097 \)), increased malpresentation (7.1% vs. 3.4%, \( p = 0.319 \)), increased placenta abruption (7.1% vs. 1.1%, \( p = 0.058 \)) and increased placental praevia (4.8% vs. 0.0%, \( p = 0.054 \)) compared to the high-risk group (Chart 12).

Chart 12 - Reasons for emergency CS.
* 2*2 Chi-square (x^2) test was used to compare obstructed labour and fetal
distress, obstructed labour combined with fetal distress, and unknown reasons. Fisher’s
exact test was used to compare placental abruption, and placenta praevia.

Data reliability: There is no missing data in this section. Some inconsistencies
were found in the medical records regarding this part of information. The reliability is
intermediate.
3.3.5 Perineal status and suture

1) Perineal status

Of the low-risk group patients who underwent vaginal delivery, 21.1% had intact perineum, 14.5% had first degree perineal laceration, 42.5% had second degree perineal laceration, 6.0% had third degree perineal laceration, 0% had forth degree perineal laceration, and 16% had lateral episiotomy. Among the high-risk group patients who did not have CS, 23.0% had intact perineum, 18.4% had first degree perineal laceration, 38.3% had second degree perineal laceration, 7.4% had third degree perineal laceration, 0.4% had forth degree perineal laceration and 12.4% had lateral episiotomy. There was no statistical difference regarding perineal status between the two groups (p=0.340) (Chart 13).

Chart 13 - Perineal status.

* Fisher’s exact test was used.
2) Perineum suture

After vaginal delivery, perineum suturing was performed in 71.9% of patients in the low-risk group and 68.1% of patients in the high-risk group. There is no statistical difference regarding the suture status between the two groups (p=0.300).
Data reliability: Information about perineal status was unavailable for 0.2% of patient in the low-risk group. Information in this section was well recorded in the medical forms. The reliability is good (Table 12).

Table 12 - Missing data of perineal status and sutured status.

<table>
<thead>
<tr>
<th></th>
<th>Low-risk Group</th>
<th>High-risk Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perineal status</td>
<td>0.2%</td>
<td>0</td>
</tr>
<tr>
<td>Sutured status</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
3.3.6 Delivery complications

Patients in the low-risk group had rates of shoulder dystocia comparable to the patients in the high-risk group (1.6% v.s. 1.5%, p=0.930), as well as of meconium liquor (4.9% v.s. 3.0%, p=0.129) (Chart 14).

Chart 14 - Delivery complications including shoulder dystocia and meconium liquor.

* 2*2 Chi-square (x²) test was used.

Data reliability: There is no missing data in this section. The information regarding delivery complications were precisely recorded in the medical forms. The reliability is good.
3.3.7 Hospitalization and after delivery bleeding

After delivery, patients in the low-risk group tended to leave the hospital earlier than the patients in the high-risk group, but this number did not achieve statistical significance (2.7 ± 1.9 days v.s. 3.0 ± 2.07 days, p= 0.052). These two groups had similar amounts of after-birth bleeding (422.8 ± 336.7 ml v.s. 444.4 ± 393.4 ml, p= 0.358) (Table 13).

Table 13 - Information regarding after delivery hospital stay and after delivery bleeding.

<table>
<thead>
<tr>
<th></th>
<th>Low-risk Group</th>
<th>High-risk Group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital stay after delivery</td>
<td>2.7 ± 1.9</td>
<td>3.0 ± 2.07</td>
<td>0.052</td>
</tr>
<tr>
<td>(days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding after delivery</td>
<td>422.8 ± 336.7</td>
<td>444.4 ± 393.4</td>
<td>0.358</td>
</tr>
<tr>
<td>(ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Student's t-test was used.
Data reliability: Missing data in the section is less than 10%. Data regarding after delivery information is well documented in the medical forms. The reliability is good (Table 13).

Table 13 - Missing data of after delivery information.

<table>
<thead>
<tr>
<th></th>
<th>Low-risk Group</th>
<th>High-risk Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital stay after delivery</td>
<td>0.4%</td>
<td>0</td>
</tr>
<tr>
<td>Bleeding after delivery</td>
<td>0.2%</td>
<td>0.4%</td>
</tr>
</tbody>
</table>
3.3.8 Summary of maternal outcomes

The most interesting finding of this audit was the significant higher rate of spontaneous preterm birth among low-risk group patients. However, the low-risk group patients had a lower rate of developing pregnancy induced-hypertension compared to the high-risk group.

Due to the different delivery strategy between the two groups, the low-risk group patients were more likely to start their labour spontaneously, while the high-risk group patients had more induced labours. Regarding the rate of having CS, patients in the low-risk group had a lower rate of elective CS. The main reasons of elective CS for both groups were repeated CS, followed by malpresentation. However, patients in the high-risk group were more likely to experience elective CS due to the suspicion of having a LGA baby. The emergency CS rate was comparable between the two groups. The reasons for emergency CS were similar between both groups, including rates of obstructed labour and fetal distress. There was also a strong trend for shorter hospital stays in patients of the low-risk group, which might be attributed to the lower CS rate.

In terms of delivery complications, the rates of shoulder dystocia were low in both groups and also were comparable with each other. Similarly, there was no difference regarding perineal status and the requirement for perineal suturing between the two groups, as well as blood loss after deliver.

In conclusion, patients in the low-risk group had significantly increased risk of preterm birth even after adjusting for multiple confounders. Patients in the low-risk group had lower prevalence of pregnancy induced hypertension, lower rate of induced
labour and a lower rate of elective CS. However, the rate of emergency CS was comparable between the two groups, as was the rate of shoulder dystocia.
3.4 Neonatal Outcomes

3.4.1 Birth status

There were two cases of stillbirth among all 975 patients (0.2%), one in each group. In the high-risk group, the mother was obese (BMI = 35.4 kg/m²) with a high GCT results (12.1 mmol/l). This baby was delivered at 37.6 weeks of gestation, with birth weight equal to 3,295 g. In the low-risk group, the mother had a normal BMI (19.5 kg/m²), but abnormal OGTT results (fasting = 4.3 mmol/l, 1h = 12.5 mmol/l and 2h = 13 mmol/l). The baby was delivered at 38.5 weeks of gestation, weighing 3,190 g. Based on their GCT and OGTT results, it is possible that both mothers who had stillbirth might have had diabetes prior to their pregnancies.
3.4.2 Apgar Score

Patients in the low-risk group had Apgar scores at 1 minute (8.2 ± 1.5 v.s. 8.3 ± 1.6, p= 0.717) and at 5 minutes (8.9 ± 0.9 v.s. 8.8 ± 1.2, p= 0.158), comparable or similar to patients in the high-risk group.

1) Apgar scores at 1 minute

Apgar scores at 1 minute were divided into three groups: low Apgar score (0-3), intermediate Apgar score (4-6) and normal Apgar score (7-10). In the low-risk group, 3.1% of patients had a low score, 14.2% had an intermediate score and 82.7% had a normal Apgar score. In the high-risk group, 3.3% had a low score, 13.7% had an intermediate score and 83.0% had a normal Apgar score. There was no statistical difference between the two groups regarding low Apgar score (p=0.947), intermediate Apgar score (p=0.853), and normal Apgar score (p=0.889) (Chart 15).

Chart 15 - proportion of three groups of Apgar score at 1 minute.
* R*C Chi-square ($x^2$) test was used.

2) Apgar score at 5 minutes

Compared to the babies of high-risk mothers, those of low-risk women had similar rates of a low score at 5 minute (0.8% vs. 1.5%, $p=0.289$), an intermediate score at 5 minute (1.4% vs. 2.8%, $p=0.174$), and a normal Apgar score at 5 minute (97.8% vs. 95.7%, $p=0.068$) (Chart 16).

Chart 16 -proportion of three groups of Apgar score at 5 minute.

* 2*2 Chi-square ($x^2$) test was used.

Data reliability: There is no missing data in this section. The information of Apgar score was well documented in the medical forms. The reliability is good.
3.4.3 Birth weight

1) Birth weight, length, and ponderal index

Compared to babies of high-risk mothers, babies born to mothers in the low-risk group had similar birth weight (3,257.7 ± 498.3 g v.s. 3,299.9 ± 503.6 g, p=0.189), birth length (49.0 ± 2.4 cm v.s. 49.0 ± 2.4 cm, p= 0.776), and ponderal Index (2.8 ± 0.3 g/cm³ v.s. 2.8 ± 0.3 g/cm³, p=0.234) (Table 15).

Table 15 -Information regarding birth weight, birth length and Ponderal Index.

<table>
<thead>
<tr>
<th></th>
<th>Low-risk Group</th>
<th>High-risk Group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight (g)</td>
<td>3,257.7 ± 498.3</td>
<td>3,299.9 ± 503.6</td>
<td>0.189</td>
</tr>
<tr>
<td>Birth length (cm)</td>
<td>49.0 ± 2.4</td>
<td>49.0 ± 2.4</td>
<td>0.776</td>
</tr>
<tr>
<td>Ponderal index (g/cm³)</td>
<td>2.8 ± 0.3</td>
<td>2.8 ± 0.3</td>
<td>0.234</td>
</tr>
</tbody>
</table>

* Student’s t-test was used.
2) Macrosomia, low birth weight, neonatal obese, neonatal underweight

Mothers in the low-risk group had comparable prevalence of macrosomic babies (5.5% v.s. 7.1%, p=0.309) and low-birth-weight babies (6.7% v.s. 5.2%, p=0.313), compared to the mothers in the high-risk group. Babies of low-risk group mothers also had similar rate of being obese (33.5% v.s. 37.7%, p=0.179) and being underweight (3.6% v.s. 4.3%, p=0.533) based on the PI value, compared to the babies born from mothers in the high-risk group (Chart 17).

Chart 17 -Information regarding macrosomia, low birth weight, neonatal obese, and neonatal underweight.

* 2*2 Chi-square (x²) test was used.
3) Customized LGA and customized SGA

The customized LGA (cLGA) and SGA (cSGA) rates were calculated by using the customised centile calculator for the Australian population, which controlled for maternal height, maternal weight, maternal ethnicity, parity, neonatal sex, and gestational age. Compared to the babies of the low-risk group patients, more infants of the high-risk group women tended to be cLGA (9.4% vs. 6.1% in the low-risk group, \(p=0.050\)), but had a comparable rate of being cSGA (13.1% v.s. 12.4% in the low-risk group, \(p=0.739\)) (Chart 18).

Chart 18 - Prevalence of cLGA and cSGA babies.
Data reliability: Birth weight had no missing data. Information in this section is precisely recorded in the medical forms. The reliability is good (Table 16).

Table 16 - Missing data for birth weight, length, ponderal index, macrosomia, low birth weight, obesity, leanness, cLGA, cSGA.

<table>
<thead>
<tr>
<th></th>
<th>Number of cases with missing data (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low-risk Group</td>
</tr>
<tr>
<td>Birth weight</td>
<td>0</td>
</tr>
<tr>
<td>Birth length</td>
<td>0.4%</td>
</tr>
<tr>
<td>Ponderal Index</td>
<td>0.4%</td>
</tr>
<tr>
<td>Macrosomia</td>
<td>0</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>0</td>
</tr>
<tr>
<td>Obesity</td>
<td>0.4%</td>
</tr>
<tr>
<td>Leanness</td>
<td>0.4%</td>
</tr>
<tr>
<td>cLGA</td>
<td>0</td>
</tr>
<tr>
<td>cSGA</td>
<td>0</td>
</tr>
</tbody>
</table>

cLGA customized large for gestational age

cSGA customized small for gestational age
3.4.4 Neonatal complications

1) Bone fracture and nerve palsy

There were two cases of bone fractures, all in babies born to high-risk patients. One case had a right humerus fracture and other case had a left humerus fracture.

Two cases of nerve palsies occurred during the study period of time: a case of facial nerve palsy in the low-risk group, and a case of Erb’s palsy in the high-risk group.
2) Hypoglycaemia, jaundice, respiratory distress and NICU/SCN admission

Babies of patients in the low-risk group had a similar prevalence of hypoglycaemia (6.1% v.s. 7.1%, p=0.532), jaundice (8.8% v.s. 10.7%, p=0.320), and respiratory distress (6.3% v.s. 6.0%, p=0.857) compared to babies of mothers in the high-risk group. Interestingly, the rate of admission into NICU/SCN was significantly higher in babies of low-risk group patients (16.7% v.s. 10.9%, p=0.010) (Chart 19).

Chart 19 - Information regarding hypoglycaemia, jaundice, respiratory distress, NICU/SCN admission.

* 2x2 Chi-square ($\chi^2$) test was used.

Data reliability: There are no missing data in this section. The neonatal complications were well recorded in the medical forms. The reliability is good.
3) Stay in the NICU/SCN and reasons for NICU/SCN admission

Babies of low-risk mothers stayed in the NICU/SCN for the same amount of time as babies of high-risk women (7.12 ± 6.67 days v.s. 8.57 ± 7.34 days, p=0.258).

Among babies of low-risk group mothers, 35.3% were admitted for prematurity, 20.0% for respiratory distress, 10.6% for hypoglycaemia, 5.9% for low Apgar score, 4.7% for prematurity combined with respiratory distress, 3.5% for congenital abnormality, 1.2% for jaundice, and 18.8% for unspecific reasons. Alternatively, among babies of high-risk group mothers, 27.5% were admitted due to prematurity, 19.6% due to respiratory distress, 17.6% due to low Apgar score, 5.9% due to hypoglycaemia, 3.9% due to prematurity combined with respiratory distress, 3.9% due to congenital abnormality, 2.0% due to jaundice, and 19.6% due to unknown reasons. Only low Apgar score was statistically different between two groups among all these reasons (5.9% v.s. 17.6%, p= 0.028) (Chart 20).
* 2*2 Chi-square ($x^2$) test was used.

NICU, neonatal intensive care unit; SCN, special care nursery
Data reliability: There were no missing data regarding the NICU/SCN admission reasons. There were 5 cases with missing information in the low-risk group about the time that babies spent in the NICU/SCN. Information in this section is well recorded in the medical forms. The reliability is good (Table 17).

Table 17 - Missing data of NICU/SCN staying time and admission reasons.

<table>
<thead>
<tr>
<th></th>
<th>Number of cases with missing data (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low-risk Group</td>
</tr>
<tr>
<td>Time stay in the NICU/SCN</td>
<td>1.0%</td>
</tr>
<tr>
<td>Reasons for NICU/SCN admission</td>
<td>0</td>
</tr>
</tbody>
</table>
3.4.5 Summary of the neonatal outcomes

The rate of serious neonatal complications was low: only two cases of stillbirth, two cases of bone fractures and two cases of nerve palsy were recorded among 975 babies born to GDM patients.

Birth weight is an important indicator of the effect of GDM treatment. Mean birth weights were comparable between the two groups. However, after adjusting for confounding factors such as gestational age, gender, maternal weight, maternal height, parity and ethnicity, high-risk group mothers tended to have an increased prevalence of LGA babies (9.4% vs. 6.1%, p=0.05). Interestingly, when measuring the ponderal index of babies born to mothers with GDM, obesity rates were similarly high in both groups. Infants of these two groups had comparable rates of macrosomia, low birth weight, SGA, and leanness.

In terms of neonatal complications, babies in these two groups had comparable rates of hypoglycaemia, jaundice, and respiratory distress. Babies of mothers in the low-risk group had a higher rate of NICU/SCN admission. The main reason for NICU/SCN admission was prematurity, followed by respiratory distress. However, babies of low-risk group patients were less likely to be admitted into NICU/SCN because of low Apgar score. The duration of the NICU/SCN stay was comparable between both groups.

In conclusion, the rate of severe neonatal complications, including stillbirth, bone fracture and nerve palsy was low in both groups. The rate of neonatal hypoglycaemia, jaundice and respiratory distress was comparable between the two
groups. Interestingly, more babies in the high-risk group tended to be LGA, and neonatal obesity, assessed by the ponderal index, was observed in babies from both groups.
3.5 NICU admission information in The Canberra Hospital

3.5.1 General Information

The rate of NICU/SCN admission was significantly lower at The Canberra Hospital compared to the Calvary Hospital (12.5% vs. 20.1%, p= 0.010). This is most likely due to differences in NICU admission policy between The Canberra hospital and the Calvary Hospital. For this reason, only an analysis of babies admitted to NICU at The Canberra Hospital was performed.

Among 786 babies born to mothers with GDM in The Canberra Hospital, 47 (14.7%) babies born to low-risk group mothers were admitted into NICU, while 51 (10.9%) babies born to high-risk group were admitted. Interestingly, the admission rates were not statistically different between the two groups (p=0.119). The length of stay in NICU was also not significantly different between the two groups (8.5 ± 6.7 days v.s. 8.6 ± 8.3 days, p= 0.941) (Table 18).

Table 18 - NICU admissions of neonates born in The Canberra Hospital.

<table>
<thead>
<tr>
<th></th>
<th>Low-risk Group</th>
<th>High-risk Group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NICU Admission</td>
<td>14.7%</td>
<td>10.9%</td>
<td>0.119</td>
</tr>
<tr>
<td>Stay in the NICU (days)</td>
<td>8.5 ± 6.7</td>
<td>8.6 ± 8.3</td>
<td>0.941</td>
</tr>
</tbody>
</table>

* 2*2 Chi-square (x²) test was used to compare the rate of NICU admission. Student’s t-test was used to compare the number of days these babies spent in the NICU.
3.5.2 Neonatal Complications

1) Neonatal Death:

In The Canberra Hospital NICU, there was one neonatal death (1%) of a baby born to a mother in the low-risk group. This infant died on the first day after being admitted into NICU, and the reason of death was a severe diaphragmatic hernia.
2) Hypoglycaemia:

In babies admitted to NICU, those born to low-risk mothers had similar prevalence of having hypoglycaemia compared to babies of high-risk group patients (36.2% vs. 51.0%, p= 0.140) (Chart 20). Furthermore, the degree of hypoglycaemia was comparable between the two groups as well (low-risk group 1.42 ± 0.64 mmol/l v.s. high-risk group 1.65 ± 0.52 mmol/l, p= 0.296). In terms of treatment options for neonatal hypoglycaemia, there was no statistical difference in requirement for intravenous glucose infusion between the two groups (low-risk group 84.6% vs. high-risk group 73.9%, p= 0.682) (Chart 21).

Chart 21 - Information regarding neonatal hypoglycaemia and its treatment in The Canberra Hospital NICU.

* 2*2 Chi-square (x²) test was used
3) Jaundice:

In babies admitted to NICU, those born to low-risk mothers with GDM had similar prevalence of developing jaundice compared to babies of high-risk group mothers (48.9% v.s. 58.8%, p = 0.417). Similarly, of the NICU babies diagnosed with jaundice, those born from mothers of the low-risk GDM group had comparable rates of needing phototherapy to those babies of the high-risk GDM group (39.1% v.s. 43.3%, p = 0.786) (Chart 22).

* 2*2 Chi-square (x²) test was used
4) Respiratory distress:

(1) Rate and main causes of respiratory distress

In babies admitted to NICU, those born to the low-risk GDM mothers had similar prevalence of having respiratory distress compared to babies of the high-risk GDM mothers (59.6% v.s. 51.0%, p=0.422). The three main causes of neonatal respiratory distress among babies of the GDM mothers who were admitted into NICU were transient tachypnoea of the newborn (TTN) (31.6%), hyaline membrane disease (HMD) (12.2%) and pneumothorax (3.1%). Babies of the NICU admitted babies of the low-risk group patients had comparable rates of TTN (36.2% v.s. 27.5%, p=0.391), HMD (14.9% v.s. 9.8%, p=0.543), and pneumothorax (2.1% v.s. 3.9%, p=1.000) compared to the babies of the NICU admitted babies of the high-risk group mother (Chart 23).
Chart 23 - Respiratory distress and causes in The Canberra Hospital NICU

* 2x2 Chi-square ($x^2$) test was used

** TTN, Transient Tachypnoes of Newborn (TTN); HMD, Hyaline Membrane Disease.
(2) Treatment of respiratory distress

For those NICU babies who had respiratory distress, those born to low-risk group women were more likely to be treated with oxygen alone, compared to babies born to high-risk group patients (17.9% v.s. 0.0%, p = 0.038). However, the uses of continuous positive airway pressure (CPAP) (60.7% v.s. 65.4%, p = 0.723), mechanical ventilation (10.7% v.s. 15.4%, p = 0.610), and expectant (observational only) treatment (10.7% vs. 19.2%, p = 0.378) were comparable between the two groups (Chart 24).

Chart 24 - The treatment options of respiratory distress in The Canberra Hospital NICU.

* 2*2 Chi-square (x^2) test was used

** CPAP, Continuous Positive Airway Pressure
5) Other main complications

In babies admitted to NICU, those of the low-risk group GDM mothers had comparable prevalence of developing other metabolic abnormalities including hyponatremia, hypernatremia, hypocalcaemia, hypophosphataemia and metabolic acidosis, compared to the babies born of the high-risk group GDM mothers (14.9% v.s. 15.7%, p= 1.000).

Babies admitted to NICU born to the low-risk compared to the high-risk group of GDM patients had similar rates of hypoxic ischemic encephalopathy (HIE) (4.3% v.s. 7.8%, p= 0.679) and coagulopathy (4.3% v.s. 7.8%, p= 0.679) (Chart 25).

Chart 25 - Other main complications in The Canberra Hospital NICU

* 2*2 Chi-square ($\chi^2$) test was used

** HIE, Hypoxic Ischemic Encephalopathy
Metabolic abnormalities include hyponatremia, hypernatremia, hypocalcaemia, hypophosphataemia and metabolic acidosis, but exclude hypoglycaemia and jaundice.

Data reliability: There is no missing data of this section. This kind of information was precisely recorded in the medical forms. The reliability is good.
3.5.3 Summary of NICU admission information

After excluding babies who were delivered in the Calvary Hospital, the rate of NICU/SCN admission in The Canberra Hospital was comparable between the two groups. This suggests that the increased rate of NICU/SCN admission in the low-risk group overall (see section 3.4.4) might be attributed to the different strategy of NICU/SCN admission between The Canberra Hospital and the Calvary Hospital. Additionally, the length of NICU/SCN stay was comparable between the two groups.

There was only one case of neonatal death due to serious malformation. The rates of hypoglycaemia were comparable between babies of mothers in both groups, as well as the degree of hypoglycaemia and the number of babies who needed intravenous glucose infusion for treatment. Similarly, the rate of jaundice and the need of phototherapy was comparable between the two groups. The three main causes of respiratory distress among babies who were admitted into NICU/SCN in The Canberra Hospital were TTN, HMD and pneumothoraces. There was no difference regarding the rates of TTN, HMD and pneumothoraces between infants of the low-risk and the high-risk group mothers. However, more babies of the low-risk group mothers who had respiratory distress were treated with oxygen alone, which might indicate that these babies had less severe forms of respiratory distress. The babies of both groups also had similar prevalence of other complications including HIE, coagulopathy and other metabolic abnormalities.

In conclusion, the infants of mothers who delivered in The Canberra Hospital requiring NICU admission from the low- and high-risk GDM groups had comparable rates
of several neonatal complications including hypoglycaemia, jaundice, and respiratory distress. However, respiratory distress in the infants of the low-risk group mothers might be less severe.
3.6 Subgroup analysis of high-risk group patients who continued diet treatment (HRD)

High-risk patients were subdivided into two groups: patients who attended the diabetes clinics and started insulin treatment (HRI), and patients who attended the multidisciplinary clinic, did not start insulin treatment, and were advised to undergo dietary treatment (HRD). The level of antenatal obstetric care of the HRD patients was higher than the low-risk group patients, but lower than the HRI patients. There were 509 patients in the low-risk group, 75 patients in the HRD group, and 391 patients in the HRI group.

3.6.1 Maternal demographic information

Patients in the HRI group were the oldest (32.8 ± 5.4 years-old), and had the highest BMI (29.7 ± 7.7 kg/m²), the most parity (1.0 ± 1.2 times), the highest rates of GDM history (25.1%) and family history of diabetes (68.7%), and the earliest diagnosis of GDM (26.5 ± 4.5 weeks) among the three groups. The HRI group had the highest percentage of patients who were Anglo-European (61.0%), but the lowest percentage of patients who were South-East Asian (8.8%). Regarding the level of glucose intolerance, the HRI group also had the highest GCT results (9.3 ± 1.6 mmol) and the highest fasting glucose levels in the OGTT (5.1±0.8 mmol/l).

Maternal demographic data of patients in the HRD group were quite similar to those of patients in the low-risk group. These two groups had comparable age, BMI, parity, GDM history, family history of diabetes, and results of GCT and OGTT. However,
patients in the HRD group met care providers earlier (11.4 ± 5.6 weeks vs. 15.1 ± 6.6 weeks, p< 0.001) and were diagnosed with GDM earlier (27.1 ± 4.0 weeks vs. 28.3 ± 2.8 weeks, p=0.007), compared to the low-risk group patients. Moreover, more HRD patients were of South-East Asian ethnic background (28.0% vs. 19.4%).

All three groups had comparable rates of smoking and alcohol consumption, as well as 1-h and 2-h OGTT results (Table 19 and Table 20).

Table 19 - Maternal demographic information for the three groups part I.

<table>
<thead>
<tr>
<th></th>
<th>Low-risk group</th>
<th>HRD group *</th>
<th>HRI group *</th>
<th>P value **</th>
<th>P value ***</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong> (years-old)</td>
<td>31.7 ± 4.8</td>
<td>31.6 ± 5.1</td>
<td>32.8 ± 5.4</td>
<td>0.006</td>
<td>0.821</td>
</tr>
<tr>
<td><strong>BMI</strong> (kg/m²)</td>
<td>26.3 ± 6.7</td>
<td>27.0 ± 5.8</td>
<td>29.7 ± 7.7</td>
<td>&lt;0.001</td>
<td>0.392</td>
</tr>
<tr>
<td><strong>Parity</strong> (times)</td>
<td>0.7 ± 1.0</td>
<td>0.7 ± 1.0</td>
<td>1.0 ± 1.2</td>
<td>&lt;0.001</td>
<td>0.844</td>
</tr>
<tr>
<td><strong>Gestational age of first antenatal</strong></td>
<td>15.1 ± 6.6</td>
<td>11.4 ± 6.0</td>
<td>13.6 ± 7.5</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Visit (weeks)</td>
<td>Gestational age when GDM was diagnosed (weeks)</td>
<td>GCT results (mmol/l)</td>
<td>Fasting OGTT results (mmol/l)</td>
<td>1-h OGTT results (mmol/l)</td>
<td>2-h OGTT results (mmol/l)</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------------------------------------------</td>
<td>----------------------</td>
<td>-----------------------------</td>
<td>--------------------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td></td>
<td>28.3 ± 2.8</td>
<td>8.9 ± 1.1</td>
<td>4.5 ± 0.5</td>
<td>9.6 ± 1.4</td>
<td>9.0 ± 1.0</td>
</tr>
<tr>
<td></td>
<td>27.1 ± 4.0</td>
<td>8.5 ± 0.7</td>
<td>4.5 ± 0.5</td>
<td>9.6 ± 1.3</td>
<td>8.9 ± 0.7</td>
</tr>
<tr>
<td></td>
<td>26.5 ± 4.5</td>
<td>9.3 ± 1.6</td>
<td>5.1 ± 0.8</td>
<td>9.8 ± 1.4</td>
<td>9.0 ± 1.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* HDR, High-risk group on diet treatment; HRI, High-risk group on insulin treatment; BMI, Body Mass Index; OGTT, Oral glucose tolerance test

** One-way ANOVA  *** Post Hoc analysis
### Table 20 - Maternal demographic information for the three groups Part II.

<table>
<thead>
<tr>
<th></th>
<th>Low-risk group</th>
<th>HRD group *</th>
<th>The HRI group *</th>
<th>P value **</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GDM history</strong></td>
<td>13.2%</td>
<td>13.3%</td>
<td>25.1%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Family history of diabetes</strong></td>
<td>55.5%</td>
<td>58.7%</td>
<td>68.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td>10.1%</td>
<td>7.1%</td>
<td>10.7%</td>
<td>0.669</td>
</tr>
<tr>
<td><strong>Alcohol consumption</strong></td>
<td>5.4%</td>
<td>4.3%</td>
<td>4.8%</td>
<td>0.890</td>
</tr>
<tr>
<td><strong>Anglo-European</strong></td>
<td>56.3%</td>
<td>46.7%</td>
<td>61.0%</td>
<td>0.055</td>
</tr>
<tr>
<td><strong>South-East Asian</strong></td>
<td>19.4%</td>
<td>28.0%</td>
<td>8.8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>South Asian</strong></td>
<td>18.0%</td>
<td>20.0%</td>
<td>21.7%</td>
<td>0.378</td>
</tr>
</tbody>
</table>

* HDR, High-risk group on diet treatment; HRI, High-risk group on insulin treatment

** Pearson Chi-square Test
Data reliability: The data reliability regarding maternal demographic data is good. However, for the GCT and OGTT results, there were a few missing data, so the reliability is intermediate (Table 21).

Table 21 - Missing data in demographic data.

<table>
<thead>
<tr>
<th></th>
<th>Low-risk Group</th>
<th>HRD Group</th>
<th>HRI Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>BMI</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Parities</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>GDM history</td>
<td>0.2%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Family history of diabetes</td>
<td>0</td>
<td>0</td>
<td>0.3%</td>
</tr>
<tr>
<td>Anglo-European</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>South- East Asian</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Gestational Age at first appointment</td>
<td>0.8%</td>
<td>0</td>
<td>0.8%</td>
</tr>
<tr>
<td>Gestational Age when diagnosed with GDM</td>
<td>1.2%</td>
<td>0</td>
<td>0.3%</td>
</tr>
<tr>
<td>GCT</td>
<td>29%</td>
<td>42.7%</td>
<td>45.5%</td>
</tr>
<tr>
<td>Fasting OGTT</td>
<td>10.4%</td>
<td>5.3%</td>
<td>15.3%</td>
</tr>
<tr>
<td>1-h OGTT</td>
<td>12.6%</td>
<td>8.0%</td>
<td>33.0%</td>
</tr>
<tr>
<td>2-h OGTT</td>
<td>12.6%</td>
<td>8.0%</td>
<td>33.2%</td>
</tr>
<tr>
<td>----------</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
</tr>
</tbody>
</table>
3.6.2 Results of HbA1c, TSH and Vitamin D

Compared to the HRI group patients, patients in the HRD group had similar results regarding HbA1c (5.3 ± 0.4 % v.s. 5.4 ± 0.5 %, p= 0.196), TSH (1.3 ± 0.9 mU/L v.s.1.2 ± 0.8 mU/L, p= 0.447), and Vitamin D (57.9 ± 21.2 ng/ml v.s. 57.3 ± 21.0 ng/ml, p= 0.887) (Table 22).

Table 22 -Results of HbA1c, TSH and Vitamin D.

<table>
<thead>
<tr>
<th></th>
<th>HRD Group</th>
<th>HRI Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>5.3 ± 0.4</td>
<td>5.4 ± 0.5</td>
<td>0.196</td>
</tr>
<tr>
<td>TSH (mU/L)</td>
<td>1.3 ± 0.9</td>
<td>1.2 ± 0.8</td>
<td>0.447</td>
</tr>
<tr>
<td>Vitamin D(ng/ml)</td>
<td>57.9 ± 21.2</td>
<td>57.3 ± 21.0</td>
<td>0.887</td>
</tr>
</tbody>
</table>

* Student’s t-test was used

** HDR, High-risk group on diet treatment; HRI, High-risk group on insulin treatment
Data reliability: Not all patients who attended the multidisciplinary clinic were required to be submitted to these tests, and some patients might have chosen to complete these tests at a pathology laboratory other than ACT pathology, which caused a few missing data in this section (Table 23). This information was extracted from CIS and clinic notes. Due to the number of missing data, the reliability of this information is low.

Table 23 - Missing data of HbA1c tests, TSH tests, and Vitamin D levels.

<table>
<thead>
<tr>
<th></th>
<th>HRD Group</th>
<th>HRI Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td>53.3%</td>
<td>9.7%</td>
</tr>
<tr>
<td>TSH</td>
<td>48.0%</td>
<td>14.8%</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>58.7%</td>
<td>29.7%</td>
</tr>
</tbody>
</table>
3.6.3 Maternal outcomes of the three groups

Patients in the HRI group had the highest prevalence of PIH (7.9%) followed by the patients in the HRD group (6.7%); patients in the low-risk group patients had the lowest prevalence (3.9%). For preeclampsia, although not statistically different, there was a similar trend among the three groups.

In terms of preterm delivery, patients in the low-risk group had the highest rate (10.6%) compared to the HRD patients (6.7%) and HRI patients (5.9%), and the difference is statistically significant (p= 0.034).

For the onset of labour, the HRD group patients were most likely to deliver spontaneously (64.0%) compared to the low-risk group patients (59.9%) and the HRI patients (20.0%). Patients in the HRI group were most likely to be induced (55.9%). Patients in the HRI group had higher rates of having an elective CS (22.3 %) compared to the HRD patients (10.7%) and the low-risk group patients (14.1%). However, these three groups of patients had comparable rates of having emergency CS. Surprisingly, in terms of the method of birth, although not statistically different, patients in the HRD group had the highest rate of instrumental vaginal deliveries compared to the low-risk group patients and the HRI group patients (HRD 22.7% vs. low-risk group 12.8% and HRI 15.3%, p= 0.081).

Shoulder dystocia was a rare event in all three groups, 8 (1.6%) cases in the low-risk group, 2 (2.7%) in the HRD group, and 5 (1.3%) in HRI group and the risk was comparable between the three groups (Table 24).
Table 24 - Maternal outcomes for the three groups.

<table>
<thead>
<tr>
<th></th>
<th>Low-risk group</th>
<th>HRD group</th>
<th>HRI group</th>
<th>P value **</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational Hypertension</td>
<td>3.9%</td>
<td>6.7%</td>
<td>7.9%</td>
<td>0.036</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>2.2%</td>
<td>2.7%</td>
<td>4.3%</td>
<td>0.166</td>
</tr>
<tr>
<td>Preterm Delivery</td>
<td>10.6%</td>
<td>6.7%</td>
<td>5.9%</td>
<td>0.034</td>
</tr>
<tr>
<td>Spontaneous onset of labour</td>
<td>59.9%</td>
<td>64.0%</td>
<td>20.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Induced onset of labour</td>
<td>23.2%</td>
<td>22.7%</td>
<td>55.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Elective CS</td>
<td>14.1%</td>
<td>10.7%</td>
<td>22.3%</td>
<td>0.002</td>
</tr>
<tr>
<td>Emergency CS</td>
<td>16.7%</td>
<td>21.3%</td>
<td>18.7%</td>
<td>0.533</td>
</tr>
<tr>
<td>Instrumental delivery</td>
<td>12.8%</td>
<td>22.7%</td>
<td>15.3%</td>
<td>0.081</td>
</tr>
<tr>
<td>Shoulder dystocia</td>
<td>1.6%</td>
<td>2.7%</td>
<td>1.3%</td>
<td>0.668</td>
</tr>
</tbody>
</table>

* HRD, High-risk group on diet treatment; HRI, High-risk group on insulin treatment

** 2*3 Chi-square Test
Data reliability: There was no missing data in this section. However, some of the results were not consistent between different medical record systems. Thus, the reliability is intermediate.
3.6.4 Neonatal outcomes of the three groups

Babies in these three groups had comparable mean birth weight. HRI patients had the highest rate of customized LGA babies (10.5%) and, although not statistically different, the lowest rate of customized SGA babies (11.5%) among the three groups. In contrast, patients in the HRD group had the lowest rate of customized LGA babies (4.0%) and they tended to have the highest rate of customized SGA babies (21.3%).

In considering ponderal index (PI), a measure of the degree of leanness or obesity of the infants, the rates of obese and thin babies were comparable among the three groups. Obesity as determined by PI, was observed in 33.5% of the low-risk group babies, 39.2% in the HDR babies, and 37.4% in HRI babies (p=0.377). Excessively lean babies were observed in 3.5% in low-risk babies, 2.7% in HRD babies, and 4.6% in HRI babies.

The rates of GDM-related neonatal complications were comparable among infants born to the three groups of patients; these complications included hypoglycaemia, jaundice, and respiratory distress. However, the rate of NICU/SCN admission was highest in infants born to the low-risk group patients (16.7%) compared to the HRD group (10.7%) and HRI group (11.0%) (Table 25).
Table 25 - Neonatal outcomes of the three groups.

<table>
<thead>
<tr>
<th></th>
<th>Low-risk group</th>
<th>HRD group *</th>
<th>HRI group *</th>
<th>P value **</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean birth weight (g)</td>
<td>3257.7± 498.3</td>
<td>3270.3± 481.8</td>
<td>3305.6± 508.0</td>
<td>0.362 ***</td>
</tr>
<tr>
<td>Customized LGA</td>
<td>6.1%</td>
<td>4.0%</td>
<td>10.5%</td>
<td>0.023</td>
</tr>
<tr>
<td>Customized SGA</td>
<td>12.4%</td>
<td>21.3%</td>
<td>11.5%</td>
<td>0.061</td>
</tr>
<tr>
<td>Obesity rate (determined by high PI)</td>
<td>33.5%</td>
<td>39.2%</td>
<td>37.4%</td>
<td>0.377</td>
</tr>
<tr>
<td>Leanness rate (determined by low PI)</td>
<td>3.5%</td>
<td>2.7%</td>
<td>4.6%</td>
<td>0.602</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>6.1%</td>
<td>4.0%</td>
<td>7.7%</td>
<td>0.664</td>
</tr>
<tr>
<td>Jaundice</td>
<td>8.8%</td>
<td>10.7%</td>
<td>10.7%</td>
<td>0.610</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>6.3%</td>
<td>6.7%</td>
<td>5.9%</td>
<td>0.951</td>
</tr>
<tr>
<td>NICU/SCN admission</td>
<td>16.7%</td>
<td>10.7%</td>
<td>11.0%</td>
<td>0.035</td>
</tr>
</tbody>
</table>

* HRD, High-risk group on diet treatment; HRI, High-risk group patients on insulin treatment; PI, ponderal index
** 2*3 Chi-square test was used

*** One-way ANOVA was used and Post Hoc test showed no statistical difference

Data reliability: There is no missing data in this section. The reliability is the same as mentioned above (good).
3.6.5 Summary of subgroup analysis of HRD group

Patients in the HRD group who went to the multidisciplinary clinic but continued diet treatment only had outcomes more similar to those of the low-risk patients, in terms of maternal demographic and antenatal information (excluding time of appointment with care provider, time of diagnosis of GDM, and ethnicity). They were clearly different to the high-risk group patients with respect to these characteristics.

Similarly, patients in the HRD group had similar prevalence of pregnancy-related complications (pregnancy-induced hypertension, preterm delivery, and shoulder dystocia) compared to the low-risk group patients. The method of delivery was also comparable between the HRD group patients and the low-risk group patients. Interestingly, the rate of instrumental delivery, although not statistically different, was higher in the HRD group compared to both the low-risk group and the HRI group.

Regarding neonatal outcomes, patients in the HRD group had the lowest rate of LGA babies and a strong trend towards having the highest rate of SGA babies among the three groups. However, the mean birth weight of infants and the rate of neonatal complications were comparable among the three groups. The difference of NICU/SCN admission could be attributed to the different NICU/SCN admission criteria of the two hospitals.

In conclusion, patients in the HRD group were more similar to the low-risk group patients in terms of maternal information, except the early appointment with care providers, early diagnosis and ethnic background. Patients in the HRD group had potentially highest rate of instrumental delivery among the three groups. Interestingly,
patients in the HRD group had the lowest prevalence of LGA babies and possibly the highest prevalence of SGA babies among three groups.
CHAPTER FOUR DISCUSSION

This research is a clinical audit to evaluate the current stratified treatment system for GDM in the ACT. According to this system, patients who are diagnosed with GDM are instructed to optimise their lifestyle and monitor their blood glucose level at home. After a one-week adjustment period, patients who are able to achieve the target glucose level only through diet and exercise are categorised into the low-risk group and receive usual antenatal care from midwives and GPs. Patients who have more than three BGL higher than the target level (which cannot be attributed to diet) are categorized into the high-risk group and are asked to attend the multidisciplinary clinic. These women are cared for by endocrinologists, obstetricians, diabetes educators, dietitians and midwives. Most patients in this category require insulin treatment to achieve the target BGL.

Compared to patients in the high-risk group, patients in the low-risk group have lower levels of antenatal surveillance and most require fewer medical resources; they do not receive specialist clinical services, nor additional ultrasound scans and blood tests. However, the glucose control of the low-risk group patient is unknown due to the lack of information on compliance of this group to lifestyle modification and self-monitoring of glucose levels.

It has been shown that, after the new IADPSG diagnostic criteria were endorsed, the prevalence of GDM in different populations did not change or increased by 3-fold (448-450). In Australia, researchers demonstrated that GDM prevalence increased from 9.6% to 13.0% if the IADPSG criteria were used instead of the ADIPS
criteria used for the period of this study (451). This high prevalence of GDM will most likely increase the burden on the already limited medical resources in Australia. The appropriate distribution of medical resources will become a major issue in the near future. It could be argued that the change in diagnostic criteria could increase the number of mild cases of GDM that could be managed within low-risk pathways. However, this may not be the case, as Duran and associates reported that GDM patients diagnosed by IADPSG criteria had comparable rates of insulin treatment compared to those diagnosed by Carpenter-Coustan (CC) criteria (450). Nevertheless, a safe mechanism to stratify women with lower risk GDM into less intensive management pathways, no matter what diagnostic criteria are used, should help with allocation of limited medical resources. Thus, it is crucial to conduct this study at this time.

This research compared the demographic features and perinatal (fetal and maternal) outcomes between the low-risk group and the high-risk group patients. The purpose of this study was to test the effectiveness of the stratification system and to access and compare the perinatal outcomes in two differently treated groups, with comparison also to the background pregnancy outcome data of the ACT. Particular focus was on safety, and therefore, the outcomes of the low-risk GDM group.

4.1 Discussion for aim one:

The first aim of this study was to test whether the stratification system actually allocated patients with fewer risk factors for adverse outcomes to the low-risk group. The results indicate that the stratification system of GDM treatment in the ACT is effective.
4.1.1 Baseline demographic information

Patients in the low-risk group had fewer risk factors associated with adverse pregnancy outcomes, including younger age, lower BMI, less parity, later gestational age of GDM diagnosis, less previous history of GDM, less family history of diabetes, and lower fasting OGTT results. There were more South-East Asian patients in the low-risk group than patients of other races.

The severity of glucose intolerance is associated with adverse outcomes. In the HAPO study, elevated fasting glucose level in OGTT tests was proven to be associated with increased risk of birth weight in the >90th percentile, primary CS, cord-blood serum C peptide >90th percentile, shoulder dystocia, and preecclampsia (83). As confirmed in previous studies, an elevated fasting BGL was also a strong predictor of insulin use. McFarland et al. even suggested that GDM patients should start insulin treatment earlier if fasting glucose levels were above 95 mg/ml (5.3 mmol/l) (452).

Similarly, pre-pregnancy obesity is a crucial risk factor for perinatal adverse outcomes. Pregnant women who are obese have increased risk of developing preeclampsia, and they are more likely to deliver a baby by induction and CS (453, 454). Moreover, they have increased risk of having a macrosomic baby (455). Researchers analysed the independent effects of maternal obesity and gestational diabetes on pregnancy outcomes, and found that obesity alone increased the risk of CS delivery (OR 2.16 95%CI 1.74-2.67), and increased the rate of macrosomic babies (OR 1.46 95%CI 0.94-2.27). Furthermore, it was found that the combination of GDM and obesity further
increased the risk of CS delivery (OR 2.26 95%CI 1.65-3.11) and delivering macrosomic babies (OR 3.45 95%CI 2.05-5.81) compared to GDM and obesity alone (456).

The ethnicity of the patient also influences perinatal outcomes. In an Australian study, authors found that GDM patients of South-East Asian ethnicity had lower average birth weight (3.08 ± 0.58kg vs.3.38 ± 0.58 kg) and lower rates of CS (17.9% vs. 28.8%) compared to women of Anglo-European ethnicity (424). Similar results were found in the USA. Sridhar and colleagues indicated that Asian women with GDM were less likely to have LGA babies compared to Caucasian patients (457). Esakoff and colleagues also demonstrated that among GDM patients, Asians had lower odds ratios for primary CS (adjusted OR 0.86 95%CI 0.77-0.96) and lower odds ratios for birth weight >4000g (adjusted OR 0.58 95%CI 0.48-0.70) compared to other ethnicities (425).

The high risk group had later diagnosis of GDM (28.3 ± 2.8 weeks v.s. 26.6 ± 4.5 weeks, p< 0.001), as well as a lower percentage of patients diagnosed with GDM before 24 weeks of gestation (6.0% v.s.18.9%, p<0.001). This difference might be caused by the local diagnostic policy. In the ACT, during the time of this study, patients who had a higher BMI, a previous GDM history, and/or a previous macrosomic baby did not require a GCT prior to an early OGTT. Considering that the low risk group women had less of these risk factors for GDM, they were less likely to be screened early. The wider range of timing of screening in the high risk group is the reason for the higher SD for the gestational age at diagnosis parameter for this group.

Unexpected, despite greater risk factors for GDM and earlier diagnosis of GDM in the high risk group, the number of women meeting diagnostic criteria for WHO diabetes in pregnancy was not higher in the high risk group. Of note, previous
researchers have shown higher rates of adverse perinatal outcomes for women diagnosed with early GDM (458). Similarly, advanced maternal age, family history of diabetes, higher parity, and previous GDM history have all been shown to be associated with multiple adverse perinatal outcomes, including increased risks for gestational hypertension, CS deliveries and LGA babies (459).

Maternal smoking and alcohol consumption are associated with increased risk of adverse perinatal outcomes, including low birth weight, preterm birth, placental abruption, and stillbirth (460-462). In this study, the rates of maternal smoking and alcohol consumption were comparable between the low-risk and high-risk groups, which is expected as the stratification was only based on whether patients could achieve target glucose levels solely through diet and exercise, within one week, rather than any criteria based on smoking or alcohol consumption.

These results are consistent with other similarly designed studies. There is no previous study that tested the efficacy of the stratification system used for GDM patients in the ACT. However, Wong and colleagues did conduct a study in New South Wales Australia, and found several risk factors for GDM patients who needed insulin treatment during pregnancy. As mentioned in section 1.7.1, there are several similarities between that study and this one, such as the diagnostic criteria, ethnic background of patients, dietary recommendations, GDM education, and more importantly, the stratification criteria (patients who exceeded target BGL on two or more occasions within 1 week were started on insulin treatment). In other words, the characteristics of insulin treated patients in the study by Wong et al. were comparable to the women in the high-risk group of this study; they also demonstrated that patients in the insulin-treated group
had higher BMI, higher fasting glucose level on OGTT, diagnosis of GDM at earlier age and were more likely to have previous GDM history (420).

The majority of the patients in the high-risk group needed insulin treatment (84%). Although these results are not directly comparable, our results were consistent with previous studies that analyzed the risk factors of insulin initiation among GDM patients. Advanced maternal age, higher BMI, a higher rate of family history of diabetes, higher rate of previous GDM history, and worse OGTT results all contributed to the increased risk of insulin use. Similarly, other studies also indicated that GDM patients who needed insulin treatment were less likely to be South–East Asian (421, 463, 464).

Interestingly, patients in the low-risk group had comparable values of the 1-h and 2-h OGTT results compared to the high-risk group patients, which might be due to the large number of 1-h and 2-h results unavailable in this study, especially in the high-risk group (12.6% in the low-risk group and 29.2% in the high-risk group). The potential explanations include: 1) patients who had previous GDM (more in the high-risk group) or other risk factors do not need to undergo a GCT, and are submitted to OGTT directly. 2) Patients who have abnormal fasting glucose levels are diagnosed with GDM prior to receiving a glucose load, which is then not given, such that the 1h or 2h tests, likely to be higher in these patients, are not performed. High-risk group patients had higher fasting glucose levels compared to the low-risk patients. And it is assumed that more patients in the high-risk group were diagnosed with GDM on elevated fasting glucose alone. 3) Some patients complete their GCT and OGTT in a pathology lab other than ACT Pathology and their results were not always recorded by their doctors in the clinic notes.
In the HAPO study, higher 1-h and 2-h glucose levels of the OGTT were related to unfavourable outcomes (83). However, in terms of the requirement of insulin treatment, some researchers found that there was no statistical difference in the 1-h and 2-h OGTT results between patients who needed insulin treatment and who did not need it (420, 463), while others showed different findings; Pertot and colleagues found that higher 1-h OGTT results were associated with increased risk of insulin treatment (421). González-Quintero and colleagues suggested that, compared to 1-h and 2-h OGTT results, 3-h BGLs of the OGTT test might have greater predictive value for the initiation of insulin treatment (463).

4.1.2 Maternal pre-existing conditions

Patients in the low-risk group had lower rates of pre-existing hypertension and hypothyroidism, but comparable rates of asthma, hyperthyroidism and PCOS.

4.1.2.1 Pre-existing hypertension

Patients in the high-risk compared to low-risk group had higher rates of pre-existing hypertension (3.4% vs. 0.6%), a complication that is associated with adverse perinatal outcomes. A recent meta-analysis encompassing 55 eligible studies and 795,221 patients demonstrated that pregnant women with chronic hypertension have an increased frequency of adverse perinatal outcomes, including superimposed preeclampsia (RR 7.7, 95%CI 5.7-10.1), CS (RR 1.3, 95%CI 1.1-1.5), pre-term birth (RR 2.7, 95%CI 1.9-3.6), low birth weight (RR 2.7, 95%CI 1.9-2.8), NICU admission (RR 3.2, 95%CI 2.2-4.4), and perinatal death (RR 4.2, 95%CI 2.7-6.5) (465). Anyaegbunan and colleagues
performed a study to compare pregnancy outcomes between GDM patients with chronic hypertension and GDM patients without hypertension. They found that infants of hypertensive GDM patients had higher birth weight, higher frequency of being LGA, and higher rates of induced delivery. There was no difference regarding the average blood glucose and frequency of SGA deliveries between the two groups (466).

Patients who have essential hypertension are also more likely to be obese and have advanced age, which were consistent with the characteristics of high-risk group patients (467). Moreover, essential hypertension is associated with increased insulin resistance that is independent of age, BMI, sex and waist-hip ratio, which may indicate patients in the high-risk group had higher levels of insulin resistance compared to the low-risk group patients (468).

4.1.2.2 Hypothyroidism

Patients in the high-risk group had a greater rate of hypothyroidism compared to the patients in the low-risk group. Hypothyroidism is known to be a risk factor for several adverse perinatal outcomes, including pregnancy-induced hypertension, intrauterine growth restriction, pre-term delivery and increased risk of CS (469-471). However, researchers demonstrated that instead of the severity of the disease itself, the treatment of hypothyroidism during pregnancy was the main factor that influenced perinatal outcomes. By receiving adequate treatment, patients with hypothyroidism were not at any increased risk for perinatal morbidity (472, 473).

The higher rate of hypothyroidism in the high-risk group patients might be attributed to undiagnosed type 1 diabetes, a higher rate of GDM history and a higher
rate of family history of diabetes among high-risk group patients. Firstly, the association between hypothyroidism and type 1 diabetes has been confirmed in the literature. Up to 30% of female patients with type 1 diabetes develop hypothyroidism (474, 475), particularly those with positive thyroid peroxidase antibodies (TPOAb) (476). It is possible that there could be undetected early type 1 diabetes patients who need insulin treatment in the high-risk group. Secondly, Vitacolonna and colleagues conducted a prospective study to analyse the association between hypothyroidism and GDM. They found that thyroid function and prevalence of thyroid disorders during pregnancy was not associated with the rate of GDM. However, they indicated a significant increase in thyroid autoimmunity in women with GDM history and hypothesized that hyperglycaemia in previous pregnancy could trigger thyroid autoimmune disorders through upregulating major histocompatibility complex (MHC) class I expression and increasing thyroid antigen presentation (477). Thirdly, researchers also found that having a family history of diabetes mellitus was associated with the increased risk of being TPOAb positive (478). All these factors could contribute to the higher rate of hypothyroidism among the high-risk group patients.

4.1.2.3 Other pre-existing maternal conditions

Maternal hyperthyroidism is associated with increased risk of preeclampsia, preterm birth, induced labour and ICU admission (479). Similarly, the pregnancies of asthmatic women are also associated with increased risk of fetal death, preterm labour, pregnancy induced hypertension, and CS (480). However, it is not surprising that the rates of maternal hyperthyroidism and asthma were comparable between the low-risk
group and the high-risk group, because the stratification was based on the patients’ glucose control within one week by diet and exercise, which is not influenced by maternal hyperthyroidism and asthma.

PCOS is associated with elevated insulin resistance and worse glucose intolerance (481, 482). Moreover, recent meta-analysis concluded that women with PCOS had a greater risk of being overweight and obese (483). Patients in the high-risk group had higher fasting glucose level and higher maternal BMI, which lead to the assumption that high-risk patients might have an increased rate of PCOS. However, the rate of PCOS was comparable between two groups (3.6% vs. 2.9%, p= 0.539). This result might be attributed to the small number of patients who had PCOS in this study or due to poor recording of this condition in the clinic notes.

4.1.3 Conclusion for aim one

The stratification system for the GDM patients that is currently applied in the ACT is effective. It allocated patients with fewer risk factors for adverse pregnancy outcomes to the low-risk group. The low-risk group patients had less advanced age, lower BMI, lower parity, later gestational age at diagnosis of GDM, lower rate of GDM history, lower rate of family diabetes, lower rate of pre-existing maternal conditions (essential hypertension and hypothyroidism), and a lower fasting glucose level in the OGTT. Additionally, more South-East Asian patients were allocated to the low-risk group, which is also related to the lower rate of adverse perinatal outcomes.
4.2 Discussion for aim two:

The second aim of this research was to compare the maternal and neonatal outcomes between the two groups, and to test the effectiveness of the stratified treatment pathways of GDM in the ACT, especially with regards to the safety of the treatment pathway of the low-risk group.

The results indicated that patients in the low-risk group had a lower rate of pregnancy-induced hypertension and were less likely to be submitted to delivery interventions. The rate of shoulder dystocia was low and comparable between the two groups. However, the low-risk group patients had significantly higher risk of spontaneous preterm delivery, which is of concern. In terms of neonatal outcomes, babies of the low-risk group patients had comparable rates of being macrosomic and having low birth weight. Although not statistically significant, there was a strong trend for low-risk patients to have fewer LGA babies, while the rates of SGA were similar among the patients of both groups. The PI, which is a better measure of leanness or obesity than birth weight, was comparable between the two groups; however, the PI results were relatively high in both groups. There was no difference between the two groups in terms of neonatal complications. The rate of NICU/SCN admission was higher in the low-risk group, which might be due to the difference in admission policy between the two hospitals, The Canberra Hospital and the Calvary Hospital.
4.2.1 Maternal outcomes:

4.2.1.1 Pregnancy induced hypertension (PIH)

Patients in this study, both in the low-risk and high-risk groups, had higher rates of PIH compared to the general population in the ACT (low-risk 6.1%, high-risk 11.8%, general population 5.7%) (484). The association between PIH and GDM has long been confirmed. A secondary analysis of the Calcium for Preeclampsia Prevention multicentre trial demonstrated that the adjusted relative risk of developing PIH among GDM patients compared with glucose tolerant women was 1.54 (95% CI 1.28-2.11) (485).

In the HAPO study, maternal hyperglycaemia was significantly associated with increased risk of preeclampsia. However, the rate of gestational hypertension was not collected in the HAPO study (83).

The low-risk group patients had a lower rate of gestational hypertension and potentially a lower rate of preeclampsia compared to the high-risk patients (6.1% vs. 11.8%), which could be attributed to lower fasting glucose levels, lower pre-gestational BMI, and lower maternal age compared to the high-risk patients. As seen in the HAPO study, an increased fasting glucose level was associated with a higher risk of preeclampsia. Thus, the higher fasting glucose level of the high-risk group patients might partially explain the increased rate of PIH compared to low-risk group women. Higher BMI and advanced maternal age are also associated with increased risk of PIH among both diabetic and non-diabetic women, independent of glucose levels (486, 487). These results are consistent with the observations of this study, that patients in the high-risk group had higher pre-gestational BMI and advanced maternal age. Insulin resistance is believed to be the underlying connection between GDM and PIH (488, 489).
However, the lower rate of PIH in the low-risk group could also be explained by the lower level of medical surveillance. The blood pressure of the high-risk group patients was checked by the care providers every time when they came to the diabetes clinic, which may have increased the detection rate of PIH. In a subgroup analysis, HRD patients who presented comparable pre-gestational BMI, maternal age and OGTT results as the low-risk group patients but received a higher level of perinatal care and had an increased rate of PIH (9.4% vs. 6.1%), which appears to support this inference. However, the rate of PIH in the HRI group was higher than the HRD group (12.2% vs. 9.4%) suggesting more a real increase in the high-risk group.

4.2.1.2 Preterm delivery

The most interesting finding in this research is that patients in the low-risk group had a significantly higher rate of preterm delivery (9.8% vs. 6.0%, p= 0.028), particularly for the rate of spontaneous preterm delivery (5.9% vs. 2.6%, p=0.011) compared to the high-risk group. The rate of preterm delivery among the general population in the ACT was 8.4% in 2011 and 8.3% in 2012 (264, 484), which is lower than the rate in low-risk group by comparison.

The exact reason for the increased risk of preterm delivery in the low-risk group is unknown, although there are several potential explanations. Firstly, compared to the high-risk group, the low-risk group patients had a lower level of perinatal care. Cao and colleagues performed a randomized study to analyse the outcomes of intensive treatment compared to standard treatment, among GDM patients. Both the intensive and the standard treatment group used the same target glucose levels and criteria of
insulin initiation. However, patients in the intensive treatment group received individualized diabetes education, lifestyle intervention and special clinic follow-ups instead of group-based diabetes education, which was used in the standard group. The difference in the level of antenatal care between the two groups in their research was similar to the difference in this study. The authors demonstrated that intensive treatment significantly reduced the risk of preterm birth (2.4% vs. 8.3%, p = 0.033). It is noteworthy that because of the comparable rate of insulin treatment, the authors concluded that the increased rate of preterm delivery was purely attributed to the lower level of antenatal care (426). The underlying mechanism that links intensive treatment and reduced risk of preterm birth could be better glucose control. Although the patients’ glucose levels during pregnancy were not available in this study, the high-risk group patients may have had better glucose control due to the more intensive treatment (490). Glucose control has been reported to be closely associated with the rate of spontaneous preterm birth in GDM patients. Yogev and colleagues demonstrated that higher mean blood glucose (p = 0.001) and lower rates of diabetes being well controlled (p = 0.004) were all significantly related to an increased risk of spontaneous preterm birth (277).

Secondly, the extra ultrasound and blood tests for high-risk patients could reduce the risk of preterm birth. The extra ultrasound tests during the third trimester might detect cervical incompetence and polyhydramnios, both of which are common risk factors of preterm delivery. Timely treatment of patients in the high-risk group may have lowered the incidence of preterm birth (491). The high-risk group patients also had checks of their full blood counts, thyroid function and Vitamin D level, which may have led to the diagnosis of thyroid dysfunction, anaemia, and vitamin D deficiency. Previous
studies indicated that overt and subclinical hypothyroidism is associated with increased risk of preterm birth, and found that the risk could be reduced by providing adequate treatment (492). Although the patients in the high-risk group had a higher rate of pre-existing hypothyroidism, this complication might be better controlled due to the more frequent clinic visits compared to the low-risk group patients. Similarly, maternal anaemia during pregnancy also increased the risk of preterm birth (493). The relationship between vitamin D deficiency and preterm birth is complicated. Vitamin D deficiency may increase a specific type of preterm birth (inflammation associated spontaneous preterm delivery) in a selective population (non-white population) (494). If patients in the high-risk group had undiagnosed hypothyroidism, anaemia or vitamin D deficiency, they would likely be detected and treated accordingly, while these complications would remain undetected in low-risk group patients and consequently, lead to the increased risk of preterm birth. However, this is only speculation at this point, as future studies would be required to prove these assertions.

Thirdly, lower BMI in the low-risk group compared to the high-risk group might contribute to the increased rate of preterm delivery. In a sub-analysis of the HAPO study, authors found that preterm delivery was less frequent with higher maternal BMI after being adjusted for several confounders and glucose levels. However, the type of preterm birth is not clearly distinguished in that study (495). Parker and colleagues conducted a cohort study and demonstrated that pre-pregnancy obesity is associated with higher risk of medically-induced preterm birth, but not spontaneous preterm delivery (496). Another meta-analysis concluded that the relationship between maternal BMI and preterm birth is complicated. The researchers found that overweight (BMI 25-
29.9 kg/m$^2$) and obese I (BMI 30-34.9 kg/m$^2$) women had a reduced risk for spontaneous preterm birth, although obese II (BMI 35-40 kg/m$^2$) and obese III (BMI >40 kg/m$^2$) women had increased risk of preterm birth (497). Overall, the relationship between maternal BMI and preterm delivery is not conclusive.

Finally, gestational weight gain (GWG) may also have played a role in increasing the risk of preterm birth in the low-risk group. In a large meta-analysis, the authors indicated that mothers with higher total GWG had lower risk of all types of preterm delivery among pregnant women (498). This study is unable to collect information regarding GWG, because it was not often recorded in the medical files. However, a majority of the patients (84%) in the high-risk group needed insulin treatment to achieve the target BGL, and previous studies in the literature suggested that insulin treatment was associated with increased GWG (499). Therefore, the low-risk group patients might have had lower GWG compared to the high-risk patients and consequently, had a higher risk of spontaneous preterm delivery.

There may be other relevant factors that contribute to the increased risk of preterm birth in the low-risk group patients, other than those mentioned above. Future studies are needed to discover the exact reason, and to develop a suitable strategy to reduce the preterm birth rate in the low-risk group.

### 4.2.1.3 Induction rate and elective CS rate

High-risk patients had higher rates of induced labours and elective CS compared to low-risk patients, which might be due to the elective delivery strategy for high-risk patients who need insulin treatment. In the ACT, high-risk patients who are
treated with insulin are likely to be induced between the 38th to 39th weeks of gestation. Additionally, if there is serious suspicion that the baby is LGA, these patients are offered an elective CS to deliver the babies. Diet-treated GDM patients are normally allowed to continue pregnancy until the spontaneous onset of labour. However, the rate of emergency CS was comparable between the two groups.

As mentioned in the introduction part, there is no consensus in terms of delivery time and method for GDM patients due to a lack of conclusive evidence. The ADA (20), the ACOG (500) in America, the NICE 2008 (501), the NICE 2013 (502) in the United Kingdom, and ADIPS (392) in Australia all have different recommendations. The advised timing of delivery for GDM patients without other complications varies from 38 completed weeks to 10 days beyond term.

Regarding the criteria for offering elective CS, ACOG suggested that it should be an option for GDM patients who have an estimated fetal weight ≥ 4500g (375). However, the ADA concluded that the role of fetal weight estimation in determining the route of delivery is unknown due to the lack of sufficient data (500).

The main benefit of elective delivery is to avoid stillbirth in later pregnancy and to reduce the risk of fetal macrosomia and shoulder dystocia. However, elective delivery may also be associated with both maternal and neonatal complications, such as the increased risk of emergency CS due to the failure of induction and increased incidence of neonatal respiratory distress and NICU admission (502). There was only one randomized controlled trial that compared the outcomes between active induction and expectant management in diabetic pregnant women who needed insulin treatment (mostly GDM patients). The authors found that the rate of CS was comparable between
the two groups, and the babies of the patients in the active induction group had lower mean birth weight and a decreased rate of being LGA. There was also no difference regarding the rate of neonatal respiratory distress including TTN and RDS between the active-induced group and the expectant-treated group (503). Similarly, in this study, high-risk patients had comparable rates of emergency CS compared to low-risk patients, and also had similar rates of neonatal respiratory distress (both TTN and RDS) and NICU/SCN admission when using the same admission criteria.

In this study, high-risk group patients had higher BMI and higher fasting glucose levels during the OGGT compared to the low-risk group patients, which may have led to an increased risk of having macrosomic babies and, consequently, shoulder dystocia. By applying the current elective delivery strategy, that is, early induction and elective CS for LGA babies, patients in the high-risk group had an acceptable rate of having macrosomic babies (7.1% vs. 5.5%, p= 0.309), as well as a low and comparable rate of shoulder dystocia, compared to the low-risk patients (1.5% vs. 1.6%, p=0.930). It is assumed that if the expectant delivery strategy had not been used in the high-risk group, more cases of macrosomia and shoulder dystocia would have occurred.

The currently elective delivery management employed in the ACT, including earlier induction and elective CS, appears to be satisfactory. It did not increase the rate of related adverse perinatal outcomes (the increased rate of emergency CS and neonatal respiratory distress), while the rates of shoulder dystocia and LGA babies were acceptable in the high-risk group patients. However, conclusive evidence of the delivery timing and method for GDM patients is still lacking.
4.2.2 Neonatal outcomes

4.2.2.1 Stillbirth

The number of stillbirths is quite low in this study. Only two cases occurred, with one in each group, among 975 deliveries (0.2%), which is even lower than the stillbirth rate in the general population (0.7% in Australia, 2011) (264). GDM is suggested to not be an independent risk factor for stillbirth (504). In both stillbirth cases, the two mothers might have had pre-existing diabetes, based on their GCT and OGTT results. This is consistent with the previous literature showing that pre-existing diabetes is associated with a higher risk of stillbirth (504, 505). The IADPSG consensus statement on the diagnosis of hyperglycaemic disorders in pregnancy advocates universal testing of pre-existing diabetes in populations with a high prevalence of type 2 diabetes during the early stage of pregnancy (506). This result also emphasized the importance of identifying overt diabetes in the early stage of pregnancy, and a recommendation from this research could be that any women diagnosed with WHO diabetes in pregnancy should always be managed within high-risk multidisciplinary teams.

4.2.2.2 Rate of customized LGA

The mean birth weight as well as the rate of macrosomia (5.5% vs. 7.1%, p= 0.309) was comparable for both the high-risk and low-risk groups. The rate of macrosomic babies in both groups was low compared to the general population in the ACT 2012 (11.8%). However, it might not represent the real fetal growth due to differences in gestational age and maternal demographic information. In this study, a customized birth weight percentile calculator that controls for maternal age, maternal
height, maternal weight, parity, and ethnicity, which are all important factors that might influence the rate of LGA and SGA in babies, was used. This calculator, obtained from the www.gestation.net website, uses the method of Gardosi and Francis, which was specifically designed for the Australian population (507). By using the customised calculator, babies defined as LGA and SGA were more closely associated with perinatal complications than LGA and SGA babies categorized by the standard population-based chart (508). In the current study, when the customised calculator was used, we observed a strong trend towards high-risk group patients having more LGA babies, when compared to the rate of LGA babies in the low-risk group (9.4% vs. 6.1%, p= 0.050).

The LGA rate in this study was reasonable compared to other studies. The rate of LGA was 9.5% in the HAPO study, which might represent the rate of LGA in the general population, due to the large number of participants and the exclusion of the mothers with significant glucose intolerance (83). There were two large randomized controlled trials aimed to demonstrate the influence of GDM treatment. Landon and colleagues found that the rate of LGA in their treated group was 7.1 %, while the rate of LGA was 13.0% among the treated group in another study conducted by Crowther and colleagues (260, 261). Although the LGA rates in this study could not be directly compared to previous studies, due to the differences in demographic characteristics of the patients, study design, diagnostic criteria and treatment strategy, we found comparable rates of LGA to those studies.

The potentially higher rate of LGA in the high-risk group could be explained by several factors. Firstly, the high-risk group patients had higher fasting glucose levels compared to patients in the low-risk group, which might contribute to the greater rate
of LGA babies. As confirmed in the HAPO study, the fasting, 1-h and 2-h OGTT results were all significantly related to the increased rate of LGA (83).

Secondly, this difference in the rate of LGA between groups could also be explained by the higher BMI of patients in the high-risk group. In a sub-analysis of the HAPO study, researchers demonstrated that higher BMI was associated with an increased risk of LGA (adjusted OR 3.31, 95%CI 2.68-4.10), independent of the patients’ glucose levels in the OGTT (509). This association was also supported by other studies (510, 511). Although the customized LGA calculation already controlled for maternal height and weight, these two factors were adjusted separately, unlike BMI, which combines both factors. Sjaarda and colleagues indicated that after excluding the adjustment of maternal weight from the customized calculator, more LGA babies were diagnosed by the modified percentile calculator, which was associated with greater rates of shoulder dystocia, NICU admission and neonatal respiratory complications. The authors suggested that the mathematic method for maternal weight adjustment in the customized calculator could be further improved (512). Therefore, the influence of elevated maternal BMI in the high-risk group may still be a potential cause of higher rates of LGA babies in this group.

Thirdly, the other possible explanation for the increased rate of LGA babies in the high-risk group is higher gestational weight gain. Lee and colleagues conducted a study to analyse the relationship between gestational weight gain, pre-pregnancy BMI and GDM with the risk of LGA. They found that compared to higher BMI and GDM status, excessive gestational weight gain (≥ 15 kg) was a more important risk factor (513). Similarly, Kim and colleagues performed a study to assess this association in a multi-
ethnic population. They indicated that for all ethnic groups, GDM contributed the least (2.0-8.0%), whereas excessive gestational weight gain contributed the most (33.3%-37.7%) to LGA rates (514). Insulin treatment was suggested to be associated with increased weight gain (499, 515). The majority of high-risk patients needed insulin treatment, which could have resulted in higher gestational weight gain, which on the one hand could contribute to the increased rate of LGA, but on the other hand by lowering BGL should reduce rates of LGA.

The results of this study are consistent with the previous literature. Barnes and colleagues conducted an epidemiologic study to evaluate the customised predictors of LGA and SGA babies in GDM patients. This study used the same diagnostic criteria of GDM, had similar target glucose levels and used the same LGA and SGA calculator. Moreover, it took place in New South Wales Australia, which has a similar ethnic background compared to the population in this study. The authors found that higher gestational weight gain, higher pre-gestational BMI and insulin treatment were all risk factors of having LGA babies diagnosed under the customised calculation (515).

4.2.2.3 Neonatal obesity rate assessed by ponderal index in both groups

In addition to birth weight, birth length is another important anthropometric measurement in neonates. In the ponderal index (PI), the neonatal weight and length are inter-related \[ \text{PI (g/cm}^3\text{)} = \frac{\text{weight (g)} \times 100}{\text{length (cm)}^3} \], and PI is an alternative measurement in newborns, because the measurement more accurately accounts for variances in height (short or tall) (516). Fetal development could be asymmetrical or symmetrical according to PI. In symmetrical neonates, an appropriate relationship
between fetal weight and length is presented by a normal PI. However, asymmetrical neonates with a high PI have relatively greater weight than length, which is taken as a measure of neonatal obesity (517). Previously, PI values higher than 2.85 g/cm$^3$ were used to define neonatal obesity, while PI values less than 2.32 was used to defined neonatal thinness (148, 447). In this research, the mean PI value, the rate of neonatal obesity and the rate of neonatal thinness were comparable between the low-risk group and high-risk group. However, the rate of obese babies was relatively high in both groups (33.5% in the low-risk group and 37.7% in the high-risk group) when compared to previous studies that showed that the neonatal obesity rate among non-diabetic women ranged from 13% to 16.5% (148, 518). However, it is possible that the assessment of neonatal obesity for Australian babies is overestimated by a PI of >2.85 g/cm$^3$, as is indicated in the study of Roje et al, who showed the 90$^{\text{th}}$ centile for PI at birth for neonates born in Croatia in the 39$^{\text{th}}$ week was higher at 3.03 g/cm$^3$ (517).

Previous research demonstrated that an increased PI value is associated with higher mean glucose value and increased High Blood Glucose Index (HBGI) (a measure of the frequency and extent of high blood glucose in continuous glucose monitoring). The parameters account for the frequency and amplitude of hyperglycaemic events during the second trimester, but not the third trimester (519). This relationship between glucose levels and glycaemic variability in the second trimester might explain why babies of GDM patients in this research had high obesity rates. Since GDM treatment is typically administered after GDM diagnosis, which occurs around 28 weeks, the treatment may be too late to reduce the PI value. Also, the current parameters used to predict fetal
growth, such as fasting glucose and postprandial glucose levels may not be sufficiently accurate as they do not dictate glucose excursions.

Maternal obesity also is a potential contributor to the elevated rate of neonatal obesity. Hill and colleagues indicated that even babies born to patients with well-controlled GDM had increased PI values, compared to babies born to non-diabetic mothers. However, after adjustments for maternal age, parity and fat mass, this difference disappeared (520). Similarly, Black and colleagues conducted a study aimed to analyse the relationship between maternal pre-pregnancy obesity, gestational weight gain, GDM status and fetal overgrowth. They demonstrated that maternal obesity, regardless of GDM status, was associated with increased neonatal PI values (455). The GDM patients in this research, both the low-risk and high-risk groups, had higher BMI than the general population in Australia in 2011 (low-risk group 26.3 kg/m² and high-risk group 29.3 kg/m² vs. 25.9 kg/m² general pregnancy women) (264), which might explain the higher rate of neonatal obesity. Similarly, although not reaching statistical difference, the rate of obesity is lower among infants born to the low-risk mothers who had lower BMI compared to the infants of high-risk mothers (33.5% vs 37.7%).

Interestingly, researchers found that there was no difference between disproportionate LGA babies (D-LGA) (PI > 90th percentile) and proportionate LGA babies (P-LGA) (PI ≤90th percentile) among GDM patients, in terms of severe neonatal complications including low Apgar score (<4 in 5 minutes), birth trauma (Erb’s palsy and fractured clavicle), hypoglycaemia, acute respiratory distress (RDS, TTN, and meconium aspiration), and hyperbilirubinaemia requiring treatment with phototherapy or exchange transfusion. However, the risk of CS was highest among D-LGA babies of
diabetic mothers (41.3%) compared to P-LGA babies of diabetic mothers (31.8%), D-LGA babies of non-diabetic mothers (24.2%), and P-LGA babies of non-diabetic mothers (18.1%) (521). Those findings are consistent with the outcomes of this study. There was no difference between the infants born to high-risk patients and infants born to low-risk mothers in terms of neonatal complications (discussed below). However, the increased rate of neonatal obesity might have contributed to the higher emergency CS rate, both the low-risk patients and the high-risk patients, compared to the general population in the ACT (low-risk group 16.7% and high-risk groups 19.1% vs. ACT general population 14.9%) (264).

4.2.2.4 Neonatal complications

The babies of low-risk patients had comparable rates of hypoglycaemia, hyperbilirubinaemia, and respiratory distress compared to the babies of high-risk patients. It is not possible to perform direct comparison regarding rates of neonatal complications between the current study and others, due to the different study populations, small numbers of cases of these complications, and varied diagnostic criteria for both GDM and neonatal complications.

The HAPO study demonstrated that the rate of clinical neonatal hypoglycaemia and the rate of hyperbilirubinaemia (treatment required) was 2.1% and 8.3%, respectively, in their study population. Compared to the HAPO study population, patients in our study had a higher rate of neonatal hypoglycaemia (low-risk group 6.3% and high-risk group 7.9%) and a higher rate of neonatal hyperbilirubinaemia (low-risk group 9.4% and high-risk group 10.9%). However, patients in this study were all GDM
patients and had worse glucose intolerance compared to participants in the HAPO study. The higher rate of maternal hyperglycaemia was associated with the increased risk of neonatal hypoglycaemia and hyperbilirubinaemia. Additionally, the diagnostic criteria of hypoglycaemia and hyperbilirubinaemia were stricter in the HAPO study, which might be why the risks of hypoglycaemia and hyperbilirubinaemia in this study were apparently higher (83).

Two milestone studies aimed at examining the effectiveness of GDM treatment have both indicated that GDM treatment might not reduce the rate of neonatal complications significantly. The Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) demonstrated lack of difference between the intervention group (under glucose monitoring, diet and insulin treatment) and the standard-care group, regarding risk of jaundice requiring phototherapy (9% vs. 9%, p=0.72), hypoglycaemia requiring IV therapy (7% vs. 5%, p= 0.16) and respiratory distress syndrome (5% vs.4%, p= 0.15) (260). Landon and colleagues also showed comparable rates of hypoglycaemia (16.3% vs. 15.4%, p= 0.75), hyperbilirubinaemia (9.6% vs. 12.9%, p= 0.12), and respiratory distress (1.9% vs. 2.9%, p=0.33) between their treated group and routine-care group (351).

Moreover, randomized controlled studies have also suggested that the type of GDM treatment and the level of antenatal care (which are the two major differences between the low-risk group and high-risk group patients in this study) did not affect the rate of neonatal complications significantly. Buchanan and colleagues conducted a RCT that aimed to compare the outcomes between diet treatment and insulin treatment in GDM patients, and they demonstrated that the rate of hypoglycaemia was similar
between the two differently treated groups (14% vs. 18%, p>0.05) (429). Similarly, another study has also indicated that the rate of hypoglycaemia (12.6% vs 14.9%, p=0.556), hyperbilirubinaemia (42.1% vs. 32.9%, p=0.118) and respiratory distress (8.7% vs. 10.9%, p=0.528) was comparable between patients who received intensive antenatal care and patients who had standard levels of antenatal care (426).

Overall, GDM treatment did not significantly reduce the rate of neonatal complications, and there was also no difference between different treatment strategies in terms of the rate of neonatal complications. The comparable rates of neonatal hypoglycaemia, hyperbilirubinaemia and respiratory distress between the low-risk and high-risk group patients are consistent with these previous findings.

The higher rate of NICU/SCN admission in the low-risk group could be attributed to the different NICU/SCN admission strategies in the two hospitals. The rate of NICU/SCN admission rate was 16.7% in the low-risk group and 10.9% in the high-risk group (p= 0.010). However, if patients delivered at the Calvary Hospital were excluded, the admission rate was comparable between the high-risk and low-risk groups (14.7% vs. 10.9%, p=0.119); babies born in the Calvary Hospital were more likely to be admitted into NICU/SCN compared to babies born in The Canberra Hospital. The rate of NICU/SCN admission rate in this study appears to be acceptable when compared to the admission rate of the general ACT population (14.7%) (484).

A smaller proportion of the babies from the low-risk group admitted into NICU/SCN were due to low Apgar scores, compared to the high-risk group (5.9% vs. 17.6%, p=0.028). Patients in the high-risk group had a higher rate of CS and pregnancy-induced hypertension; both conditions have been shown to be associated with
increased risk of low neonatal Apgar scores (522). The rate of preterm birth, which is also an important risk factor, did not have a remarkable influence on the rate of low neonatal Apgar scores due to the relatively small number of preterm births (523).

The infants who were admitted into NICU had comparable rates of hypoglycaemia, hyperbilirubinaemia and respiratory distress between the two groups, as well as neonatal complications such as hypoxic ischemic encephalopathy and coagulopathy. Furthermore, babies of both groups had similar rates of needing intravenous glucose infusion treatment for hypoglycaemia and phototherapy for hyperbilirubinaemia. Interestingly, in spite of the comparable rates of needing CPAP and mechanical ventilation for respiratory distress, the low-risk group patients were more likely to be treated with oxygen alone. The difference in the treatment of respiratory distress might have been due to the lower rate of low Apgar scores in the babies of the low-risk group patients. It might also indicate that babies in the low-risk group had a lower incidence of severe respiratory distress.

**4.2.4 Analysis of patients in the high-risk group who continued diet treatment alone (HRD)**

This research also identified a subgroup of patients (HRD group) who belonged to the high-risk group (entering the multidisciplinary clinic) but continued diet treatment to the end of the pregnancy. Patients in the HRD group had characteristics that were generally more similar to those of low-risk patients in terms of maternal age, BMI, gestation, parity, GDM history, family history of diabetes, and GCT and OGTT results (both fasting and 2-h results). However, HRD patients had earlier appointments with care providers during pregnancy, and were diagnosed with GDM at earlier stages,
when compared to low-risk women. Additionally, the percentage of patients with South-East Asian backgrounds was highest in the HRD group (HRD group 28% vs. low-risk group 19.1% and HRI group 8.7%).

The earlier appointment with care providers and the earlier diagnosis of GDM among HRD patients could indicate that they have more risk factors related to the development of GDM and other complications, or have higher GCT results that could lead to the omission of OGTT. However, the similar maternal demographic information and comparable GCT results between the HRD and low-risk group patients did not support this assumption. Another explanation for this phenomenon is that patients in the HRD group might be more compliant with medical advice during pregnancy, which also indicates that these patients might pay more attention to their health and take greater care of themselves. The earlier diagnosis of GDM might have influenced the treatment decision made by the endocrinologist. The specialists might give patients more time to adapt to the lifestyle treatment if patients had earlier GDM diagnosis, instead of starting insulin treatment immediately because of the limited treatment time.

The ethnic difference was also consistent with the previous literature. Wong and colleagues indicated that South-East Asian patients had the lowest rate of insulin treatment compared to GDM patients from other ethnicities (South-East Asian 37.2%, South Asian 55%, and Anglo-European 56.7%, p<0.001) (424).

In terms of perinatal outcomes, the patients in the HRD group had similar rates of spontaneous delivery, induced labours, and CS as low-risk patients. They had middling rates of pregnancy-induced hypertension and preterm delivery amongst the
three groups. Further, the rate of neonatal complications was similar among the three groups.

The patients in the HRD group had the lowest rate of LGA babies among the three groups (HRD 4.0% vs. low-risk group 6.1% and HRI 10.5%, p= 0.023). Paradoxically, their rate of assisted vaginal delivery was the highest and approached statistical significance (HRD 22.7% vs. low-risk group 15.3% and HRI 12.8%, p=0.081). A possible explanation for this phenomenon could be that there were more South-East Asian patients in the HRD group, whom are more likely to experience instrumental delivery compared to other ethnicities (524, 525). The exact cause of the increased risk of instrumental delivery among South-East Asian patients who had lower rate of having LGA babies compared to other ethnicities (424) is unknown. However, researchers found that there was a strong trend towards shorter mean perineal length in normal Asian pregnant women when measured in the first stage of labour, compared to Caucasian women (3.6±0.09 cm vs. 3.7±0.09, p=0.06), which might be the cause of the increased rate of instrumental delivery in the Asian population (526).

Even after adjustments for maternal weight, maternal height and ethnicity, the HRD group still had the highest rate of having SGA babies, approaching statistical significance (HRD 22.7% vs. low-risk group 15.3% and HRI 12.8%, p=0.061). One possible reason for the increased rate of SGA babies in the HRD group could be insufficient gestational weight gain. The maternal weight gain during pregnancy has been shown to be inversely associated with increased risk of having SGA babies in GDM patients (515). It is likely that some of the HRD patients were advised that insulin treatment would be necessary if their glucose levels did not improve quickly, which might have led to HRD
patients excessively restricting their food intake to avoid the use of insulin. On the other hand, some of the HRD patients may have been asked to attend the multidisciplinary clinic due to concerns of the health professionals that they were too restrictive on food intake. Furthermore, as discussed before, patients in the HRD group are more likely to stick to the medical advice and pay more attentions to their health, which might also result in unnecessary food restriction. Insufficient food intake could have led to reduced maternal weigh gain during pregnancy, and subsequently caused the highest rate of SGA babies.

**4.2.5 Conclusion for aim two:**

Patients in the low-risk group had comparable rates of stillbirth, macrosomia, shoulder dystocia, as well as a lower rate of pregnancy induced hypertension, LGA, and CS, which indicates that the treatment pathway of the low-risk group is promising. However, the higher rate of preterm delivery in the low-risk group is concerning, such that further assessment and optimisation of the low risk pathway is necessary.

As discussed before, it is also reasonable to continue elective delivery in the high-risk group patients who need insulin treatment until more conclusive evidence is available. That approach most likely leads to more acceptable rates of macrosomic babies and shoulder dystocia. Furthermore, the elevated rate of neonatal obesity observed as assessed by ponderal index in both groups needs further analysis, including analysis of cut-points for the Australian population. Finally, the high rate of SGA babies among HRD patients also needs to be addressed.
4.3 Advantages and limitations

4.3.1 Advantages:

1) This is the first clinical audit that evaluates the effectiveness of the current GDM care system used in the ACT, Australia, which has collected data from the two largest public hospitals in the region, i.e. The Canberra Hospital and the Calvary Hospital.

2) To the best of our knowledge, this is the first study that compares the perinatal outcomes in the low-risk group and the high-risk group, categorized according to whether the patients attended the multidisciplinary diabetes clinic. This information could further complete the knowledge map regarding GDM treatment.

3) This is a relatively large study. It included 975 patients diagnosed with GDM from 01/01/2010 to 30/06/2014. The number of patients fulfilled the requirements of sample size to detect a 100g difference in neonatal birth weight between the two groups.

4) A special group of patients who needed to attend the multidisciplinary clinic but managed to control their glucose level only through lifestyle treatment was identified in this research. These patients had the lowest risk of having LGA babies, but the highest risk of having SGA babies, which may indicate that these patients may have over-restricted their food intake to avoid insulin treatment.

5) The original medical records and electronic information systems were accessed. All important information was double checked, which increased the accuracy of the results.

6) This research was able to provide detailed information regarding reasons for elective CS and emergency CS, NICU admission information, and treatments for neonatal complications.
4.3.2 Limitations and future studies

1) This is a retrospective study, which can only identify the association between treatment and outcomes, but not the causal relationship. Because of the retrospective design, the information regarding the control of the glucose level, gestational weight gain, and the compliance of lifestyle management that are all crucial contributors to perinatal outcomes was not available. A future prospective study is needed, especially for identifying the cause of increased pre-term delivery in low-risk patients.

2) Due to the retrospective nature of the study, it was not possible to identify clearly the women that were initially designated as low risk, but were later referred to the DIP-MDC. For this reason, all of these women were assessed as being in the high-risk group. This did not allow an “intention to treat” analysis of the initial designation of risk.

3) This study did not include the information of GDM patients who delivered in private hospitals because of the limited study time and resources. However, it will be interesting to compare the demographic data and perinatal outcomes of private hospital patients with patients treated in public hospitals. This would be expected to provide a more comprehensive perspective in terms of the GDM treatment system in the ACT.

4) There is no control group of untreated GDM patients in this study. However, the main aim of this study was to compare the outcomes between the low-risk and the high-risk group patients. The maternal and neonatal information of the background...
population in Australian and from other relevant researches was included in this study to create a more complete picture.

4.3.3 Suggestions for the improvement of the current treatment system

1) The exact reason for the increased risk of preterm birth in the low-risk group patients is unknown. However, previous research indicated that increasing the level of antenatal care could reduce the risk of preterm delivery (426). Thus, an additional appointment with a diabetes educator or dietitian could be beneficial to further document glycaemic control, adequacy of nutrition and potential need for insulin therapy. The patients’ glucose control and gestational weight gain, which are both factors that are related to the risk of preterm birth need to be closely monitored during an additional appointment (277, 498). Regarding obstetric surveillance, the meta-analysis did not demonstrate sufficient evidence to endorse a specialised antenatal clinic for the prevention of preterm birth (527), however, there is no harm in providing improved education for low-risk group patients, especially about the signs of preterm labour. Whether it is necessary to have extra ultrasound for cervical assessment and blood tests for detection of maternal anaemia, thyroid dysfunction and vitamin D deficiency is still unknown. Further research and cost-effectiveness analyses are required.

2) Pre-gestational obesity is associated with several perinatal adverse outcomes, such as increased rates of pregnancy induced hypertension and greater risk of having neonatal overgrowth (528). In a recent systematic review of the risks associated with obesity in pregnancy, the authors suggested that women with obesity need support to lose weight before pregnancy, to reduce the rate of adverse perinatal
A special clinic for overweight and obese women who plan to have a baby in the near future might be advisable. Information about the influence of obesity on perinatal outcomes and individualized plans for weight loss should be provided.

3) Patients in the HRD group had the highest risk of having SGA babies, which might be due to the excessive food restriction. Instead of being referred back to normal antenatal care, they might need follow-up sessions with a dietitian. The importance of adequate food intake should be re-emphasized and weight gain should be assessed during these sessions. Further attention should be paid to determining the timing and delivery method of the HRD group patients to avoid unnecessary instrumental delivery.

4) The patients’ ethnicities in this study were broadly classified according to the self-reported country of birth that does not always accurately reflect ethnicity. It would be helpful if future data collection included a field for self-reported ethnicity, as well as country of birth.

4.4 Final Conclusion:

The stratification system of GDM patients in ACT is effective, as it allocates patients who have fewer risk factors and lower fasting glucose levels in the OGTT that are related to the adverse pregnancy outcomes into the low-risk group. The treatment pathway of low-risk group GDM patients, although associated with some less adverse outcomes such as pregnancy-induced hypertension, delivery interventions and cLGA neonates, several neonatal outcomes were not less. Furthermore, some neonatal outcomes were higher than in the ACT background population. For these reasons, the low risk pathway has merit, but further assessment and optimisation are required. One
optimisation could be the exclusion of women with WHO diabetes in pregnancy from the low risk group, as one women in the low risk group with WHO diabetes in pregnancy had a stillbirth. In particular, the increased rate of spontaneous pre-term birth warrants attention. The earlier delivery strategy for the high-risk patients should be continued.
Appendix
Appendix 1 Ethical approval letter from The Canberra Hospital

Professor Chris Nolan
Endocrinology Research
Building 10 Level 6
Canberra Hospital
Garran ACT 2605

Dear Professor Nolan

Re: ETHLR.12.302

The ACT Health Human Research Ethics Committee's Low Risk Sub-Committee received notification of the proposed study:

Is the strategy for care of “low risk” women with gestational diabetes mellitus really safe? at its meeting of 12 December 2012

I am pleased to inform you that your application has been approved.

The Sub-Committee agreed that the application is for low risk research and determined that the research meets the requirements of the National Statement on Ethical Conduct in Human Research and is ethically acceptable.

I attach for your records an Outcome of Consideration of Protocol form.

I confirm that the ACT Health Human Research Ethics Committee is constituted according to the National Statement on Ethical Conduct in Human Research 2007 and is certified for single review of multi-centre clinical trials. ACT Health HREC operates in compliance with applicable regulatory requirements and the International Conference on Harmonization Guidelines on Good Clinical Practice.

Yours sincerely

[Signature]

Professor John SG Biggs MA MD
FRCOG FRANZCOG DHMSA
Chairman
ACT Health Human Research Ethics Committee
Low Risk Sub Committee
12 December 2012
ACT HEALTH HUMAN RESEARCH ETHICS COMMITTEE

Outcome of Consideration of Protocol

Submission No: ETHLR.12.302  Date of Approval:  12 December 2012

Project Title: Is the strategy for care of “low risk” women with gestational diabetes mellitus really safe?

Submitted by: Professor Chris Nolan

Your project was considered by the ACT Health Human Research Ethics Committee and Approved for a period of 3 years.

First Annual Review due: December 2013

The Ethics Committee require as part of the review process that:

- At regular periods, and not less frequently than annually, Principal Investigators are to provide reports on matters including:
  - security of records
  - compliance with approved consent procedures and documentation
  - compliance with other approved procedures.
  - as a condition of approval of the protocol, that Investigators report immediately:
    - adverse affects on subjects
    - proposed changes in the protocol
    - unforeseen events that might affect continued ethical acceptability of the project.

- All published reports to carry an acknowledgement stating:
  - approved on 12 December 2012 by the ACT Health Human Research Ethics Committee.

Professor John SG Biggs, Chairman  12 December 2012
Appendix 2 Ethical approval letter from the Calvary Hospital

02-Sep-2014

Yan Zhang
Room F275 Toad Hall
30 Kinsley St, ANU
ACTON, ACT 2601

Dear Yan,

Re: 28-2014 Is the strategy for care of "low-risk" women with Gestational Diabetes Mellitus really safe?

I am pleased to advise that the Calvary Executive Management Group has approved your study 'Is the strategy for care of "low-risk" women with Gestational Diabetes Mellitus really safe?' on the recommendation of the Human Research Ethics Committee (HREC), which met out of session on 22 August 2014 to consider this project.

Approval is granted from 22nd August 2014.

If your research continues past the anticipated completion date (19 June 2015) stated in the application, it is expected that you will seek continued approval from the Human Research Ethics Committee.

Please note that the Committee requires annual reports on the progress of your research. Reports should include:
- Progress to date (or outcome in the case of completed research)
- Maintenance and security of records
- Compliance with the approved protocol
- Compliance with any conditions of approval

The Committee also requires an immediate report in any of the following events:
- Any serious or unexpected adverse effect on participants
- Any proposed changes to the protocol
- Any unforeseen events that might affect continued ethical acceptability of the project
- Discontinuation of the project before the expected date of completion
- Any change in status of the researcher (e.g. change in employment)
An electronic reporting template is available on our website. Failure to submit reports will result in your approval being suspended or cancelled.

Please note that approval is for a maximum three year period. If your research continues past a three year period it is a requirement that you reapply to the Human Research Ethics Committee for continued approval. Your date for renewal of application is 23 August 2017.

Should you wish to publish your project and Calvary Health Care ACT is in any way identified, the Committee requires that you submit your paper for HREC approval prior to publication.

Yours sincerely,

Dr John Vinen
Chair, Human Research Ethics Committee
Calvary Health Care ACT
Appendix 3 Indicators for Initiating Phototherapy

Indicators for Initiating Phototherapy
Phototherapy treatment commences when the serum bilirubin reaches maximum levels for the appropriate gestation and age in hours, when plotted on an appropriate graph (as per the birth weight based/gestational age graphs and guidelines of the American Association of Pediatrics, 2004). See Neonatal Phototherapy Record charts below

Term Infants without Haemolytic Disease

<table>
<thead>
<tr>
<th>Total Serum Bilirubin (mmol/L)</th>
<th>Consider Exchange Transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>If &gt; 1500 mg/dL</td>
</tr>
<tr>
<td></td>
<td>If &gt; 1500 mg/dL</td>
</tr>
<tr>
<td></td>
<td>Reduce if unwell,</td>
</tr>
<tr>
<td></td>
<td>asphyxia,</td>
</tr>
<tr>
<td></td>
<td>acidosis, infection</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total Serum Bilirubin (mmol/L)</th>
<th>Consider Exchange Transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>If &gt; 1500 mg/dL</td>
</tr>
<tr>
<td></td>
<td>If &gt; 1500 mg/dL</td>
</tr>
<tr>
<td></td>
<td>Reduce if unwell,</td>
</tr>
<tr>
<td></td>
<td>asphyxia,</td>
</tr>
<tr>
<td></td>
<td>acidosis, infection</td>
</tr>
</tbody>
</table>

Infants with Rhesus Disease and Premature

<table>
<thead>
<tr>
<th>Total Serum Bilirubin (mmol/L)</th>
<th>Consider Exchange Transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>If &gt; 1500 mg/dL</td>
</tr>
<tr>
<td></td>
<td>If &gt; 1500 mg/dL</td>
</tr>
<tr>
<td></td>
<td>Reduce if unwell,</td>
</tr>
<tr>
<td></td>
<td>asphyxia,</td>
</tr>
<tr>
<td></td>
<td>acidosis, infection</td>
</tr>
</tbody>
</table>

In Tradition of the Sisters of the Little Company of Mary with values Of Hospitality, Healing, Stewardship & Respect
Reviewed 2013.
Appendix 4 The number of patients who presented as percentage in the results (part one)

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Low-risk group</th>
<th>High-risk group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal baseline demographic information (low-risk group n= 509, high-risk group n= 466)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of GDM</td>
<td>67 (13.2%)</td>
<td>108 (23.2%)</td>
</tr>
<tr>
<td>Family history of diabetes</td>
<td>282 (55.4%)</td>
<td>312 (67.0%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>49 (10.1%)</td>
<td>43 (10.1%)</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>26 (5.4%)</td>
<td>20 (4.7%)</td>
</tr>
<tr>
<td>Anglo-European</td>
<td>282 (56.3%)</td>
<td>271 (58.7%)</td>
</tr>
<tr>
<td>South-East Asian</td>
<td>97 (19.4%)</td>
<td>55 (11.9%)</td>
</tr>
<tr>
<td>South Asian</td>
<td>90 (18%)</td>
<td>99 (21.4%)</td>
</tr>
<tr>
<td>Pacific Islander</td>
<td>8 (1.6%)</td>
<td>5 (1.1%)</td>
</tr>
<tr>
<td>Middle-Eastern</td>
<td>6 (1.2%)</td>
<td>8 (1.7%)</td>
</tr>
<tr>
<td>Other ethnicity</td>
<td>18 (3.6%)</td>
<td>24 (5.2%)</td>
</tr>
<tr>
<td>Essential hypertension</td>
<td>3 (0.6%)</td>
<td>16 (3.4%)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>23 (4.5%)</td>
<td>36 (7.7%)</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>3 (0.6%)</td>
<td>4 (0.9%)</td>
</tr>
<tr>
<td>Asthma</td>
<td>19 (3.7%)</td>
<td>22 (4.7%)</td>
</tr>
<tr>
<td>PCOS</td>
<td>15 (2.9%)</td>
<td>17 (3.6%)</td>
</tr>
<tr>
<td>Maternal outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational hypertension</td>
<td>36 (3.9%)</td>
<td>20 (7.7%)</td>
</tr>
<tr>
<td><strong>Maternal outcomes</strong></td>
<td><strong>Elective CS mode of delivery</strong></td>
<td><strong>Emergency CS mode of delivery</strong></td>
</tr>
<tr>
<td>-----------------------</td>
<td>----------------------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>(low-risk group n= 509, high-risk group n= 466)</td>
<td>72 (14.1%)</td>
<td>95 (20.4%)</td>
</tr>
<tr>
<td><strong>Preeclampsia</strong></td>
<td>11 (2.2%)</td>
<td>19 (4.1%)</td>
</tr>
<tr>
<td><strong>Pregnancy induced hypertension</strong></td>
<td>47 (6.1%)</td>
<td>39 (11.8%)</td>
</tr>
<tr>
<td><strong>Preterm birth</strong></td>
<td>50 (9.8%)</td>
<td>28 (6.0%)</td>
</tr>
<tr>
<td><strong>Spontaneous preterm birth</strong></td>
<td>31 (60.2%)</td>
<td>12 (43.3%)</td>
</tr>
<tr>
<td><strong>Induced preterm birth</strong></td>
<td>5 (10.2%)</td>
<td>6 (21.7%)</td>
</tr>
<tr>
<td><strong>Preterm birth without labour</strong></td>
<td>14 (29.6%)</td>
<td>10 (35%)</td>
</tr>
<tr>
<td><strong>Spontaneous onset of labour</strong></td>
<td>305 (59.9%)</td>
<td>126 (27%)</td>
</tr>
<tr>
<td><strong>Induced onset of labour</strong></td>
<td>118 (23.2%)</td>
<td>236 (23.2%)</td>
</tr>
<tr>
<td><strong>Onset of no labour</strong></td>
<td>86 (19.6%)</td>
<td>104 (22.3%)</td>
</tr>
<tr>
<td><strong>Spontaneous mode of delivery</strong></td>
<td>265 (52.1%)</td>
<td>102 (21.9%)</td>
</tr>
<tr>
<td><strong>Induced mode of delivery</strong></td>
<td>87 (17.1%)</td>
<td>180 (38.6%)</td>
</tr>
<tr>
<td>high-risk group n= 466)</td>
<td>Normal vaginal delivery</td>
<td>274 (53.8%)</td>
</tr>
<tr>
<td>-------------------------</td>
<td>-------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td></td>
<td>Forceps</td>
<td>44 (8.6%)</td>
</tr>
<tr>
<td></td>
<td>Vacuum extractors</td>
<td>34 (6.7%)</td>
</tr>
<tr>
<td></td>
<td>Delivered by CS</td>
<td>157 (45.9%)</td>
</tr>
</tbody>
</table>

**Reasons for the elective CS**

|                         | Repeated CS             | 39 (54.2%) | 57 (60.0%) |
|                         | Malpresentation          | 11 (15.3%) | 14 (14.7%) |
|                         | IUGR                    | 1 (1.4%)   | 1 (1.1%)   |
|                         | Placenta praevia        | 6 (8.3%)   | 3 (3.2%)   |
|                         | LGA                     | 1 (1.4%)   | 4 (4.2%)   |
|                         | Un-specific reasons     | 14 (19.4%) | 16 (16.8%) |

**Reasons for the emergency CS**

<p>|                         | Obstructed labour       | 23 (27.4%) | 34 (38.2%) |
|                         | Fetal distress          | 32 (38.1%) | 33 (37.1%) |
|                         | Obstructed labour       | 6 (7.1%)   | 14 (15.7%) |
|                         | combined with fetal     |             |             |
|                         | distress                |             |             |
|                         | Malpresentation          | 6 (7.1%)   | 3 (3.4%)   |
|                         | Placental abruption      | 6 (7.1%)   | 1 (1.1%)   |
|                         | Placental praevia       | 4 (4.8%)   | 0 (0.0%)   |
|                         | Un-specific reasons     | 8 (8.4%)   | 4 (4.5%)   |</p>
<table>
<thead>
<tr>
<th>Perineal status</th>
<th>Low-risk group (n=509)</th>
<th>High-risk group (n=466)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intact</td>
<td>74 (21.1%)</td>
<td>64 (23%)</td>
</tr>
<tr>
<td>First degree laceration</td>
<td>51 (14.5%)</td>
<td>55 (18.4%)</td>
</tr>
<tr>
<td>Second degree laceration</td>
<td>149 (42.5%)</td>
<td>107 (38.2%)</td>
</tr>
<tr>
<td>Third degree laceration</td>
<td>21 (6%)</td>
<td>21 (7.4%)</td>
</tr>
<tr>
<td>Forth degree laceration</td>
<td>0 (0%)</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>Lateral episiotomy</td>
<td>56 (16%)</td>
<td>35 (12.4%)</td>
</tr>
<tr>
<td>Perineum suture</td>
<td>253 (71.9%)</td>
<td>190 (68.1%)</td>
</tr>
<tr>
<td>Shoulder dystocia</td>
<td>8 (1.6%)</td>
<td>7 (1.5%)</td>
</tr>
<tr>
<td>Meconium liquor</td>
<td>25 (4.9%)</td>
<td>14 (3.0%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neonatal outcomes</th>
<th>Apgar score for 1 minute</th>
<th>Apgar score for 5 minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td>(low-risk group n=509, high-risk group n=466)</td>
<td>Low Apgar score (0-3)</td>
<td>16 (3.1%)</td>
</tr>
<tr>
<td></td>
<td>Intermediate Apgar score (4-6)</td>
<td>72 (14.2%)</td>
</tr>
<tr>
<td></td>
<td>Normal Apgar score (7-10)</td>
<td>421 (82.7%)</td>
</tr>
<tr>
<td></td>
<td>Low Apgar score (0-3)</td>
<td>4 (0.8%)</td>
</tr>
<tr>
<td>Condition</td>
<td>Row 1 Count (%)</td>
<td>Row 2 Count (%)</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>-----------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Intermediate Apgar score (4-6)</td>
<td>7 (1.4%)</td>
<td>13 (2.8%)</td>
</tr>
<tr>
<td>Normal Apgar score (7-10)</td>
<td>498 (97.8%)</td>
<td>446 (95.7%)</td>
</tr>
<tr>
<td>Macrosomia</td>
<td>28 (5.5%)</td>
<td>33 (7.1%)</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>34 (6.7%)</td>
<td>24 (5.2%)</td>
</tr>
<tr>
<td>Being obesity</td>
<td>170 (33.5%)</td>
<td>174 (37.7%)</td>
</tr>
<tr>
<td>Being underweight</td>
<td>18 (3.6%)</td>
<td>20 (4.3%)</td>
</tr>
<tr>
<td>Customized LGA</td>
<td>31 (6.1%)</td>
<td>44 (9.4%)</td>
</tr>
<tr>
<td>Customized SGA</td>
<td>63 (12.4%)</td>
<td>61 (13.1%)</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>31 (6.1%)</td>
<td>33 (7.1%)</td>
</tr>
<tr>
<td>Jaundice</td>
<td>45 (8.8%)</td>
<td>50 (10.7%)</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>32 (6.3%)</td>
<td>28 (6.0%)</td>
</tr>
<tr>
<td>NICU/SCN admission</td>
<td>85 (16.7%)</td>
<td>51 (10.9%)</td>
</tr>
<tr>
<td>NICU/SCN admission reasons</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prematurity</td>
<td>30 (35.3%)</td>
<td>14 (27.5%)</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>17 (20.0%)</td>
<td>10 (19.6%)</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>9 (10.6%)</td>
<td>3 (5.9%)</td>
</tr>
<tr>
<td>Low Apgar score</td>
<td>5 (5.9%)</td>
<td>9 (17.6%)</td>
</tr>
<tr>
<td>Condition</td>
<td>Low-risk, n=47</td>
<td>High-risk, n=51</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>----------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Prematurity combined with respiratory distress</td>
<td>4 (4.7%)</td>
<td>2 (3.9%)</td>
</tr>
<tr>
<td>Congenital abnormality</td>
<td>3 (3.5%)</td>
<td>2 (3.9%)</td>
</tr>
<tr>
<td>Jaundice</td>
<td>1 (1.2%)</td>
<td>1 (2.0%)</td>
</tr>
<tr>
<td>Un-specific reason</td>
<td>16 (18.8%)</td>
<td>0 (19.6%)</td>
</tr>
<tr>
<td>NICU/SCN admission rate</td>
<td>47 (14.7%)</td>
<td>51 (10.9%)</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>17 (36.2%)</td>
<td>26 (51.0%)</td>
</tr>
<tr>
<td>Hypoglycaemia need infusion</td>
<td>14 (84.6%)</td>
<td>19 (73.9%)</td>
</tr>
<tr>
<td>Jaundice</td>
<td>23 (48.9%)</td>
<td>30 (58.8%)</td>
</tr>
<tr>
<td>Jaundice need phototherapy</td>
<td>9 (39.1%)</td>
<td>13 (43.3%)</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>28 (59.6%)</td>
<td>26 (51.0%)</td>
</tr>
<tr>
<td>Transient tachypnoes</td>
<td>17 (36.2%)</td>
<td>14 (27.5%)</td>
</tr>
<tr>
<td>Hyaline membrane disease</td>
<td>7 (14.9%)</td>
<td>5 (9.8%)</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>1 (2.1%)</td>
<td>2 (3.9%)</td>
</tr>
<tr>
<td>Treatment for neonatal respiratory distress</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxygen</td>
<td>5 (17.9%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Condition</td>
<td>Group A</td>
<td>Group B</td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>-----------</td>
<td>-----------</td>
</tr>
<tr>
<td>Continuous positive airway pressure</td>
<td>17 (60.7%)</td>
<td>17 (65.4%)</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>3 (10.7%)</td>
<td>4 (15.4%)</td>
</tr>
<tr>
<td>Un-specific treatment</td>
<td>3 (10.7%)</td>
<td>5 (19.2%)</td>
</tr>
<tr>
<td>Other metabolic abnormality</td>
<td>7 (14.9%)</td>
<td>8 (15.7%)</td>
</tr>
<tr>
<td>Hypoxic ischemic encephalopathy</td>
<td>2 (4.3%)</td>
<td>4 (7.8%)</td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>2 (4.3%)</td>
<td>4 (7.8%)</td>
</tr>
</tbody>
</table>
### Appendix 5 The number of patients who presented as percentage in the results (part two)

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Low-risk group (n= 509)</th>
<th>HRD group (n= 75)</th>
<th>HRI group (n= 391)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maternal demographic information</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GDM history</td>
<td>67 (13.2%)</td>
<td>10 (13.3%)</td>
<td>98 (25.1%)</td>
</tr>
<tr>
<td>Family history of diabetes</td>
<td>282 (55.5%)</td>
<td>44 (58.7%)</td>
<td>268 (68.7%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>49 (10.1%)</td>
<td>5 (7.1%)</td>
<td>38 (10.7%)</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>26 (5.4%)</td>
<td>3 (4.3%)</td>
<td>17 (4.8%)</td>
</tr>
<tr>
<td>Anglo-European</td>
<td>282 (56.3%)</td>
<td>35 (46.7%)</td>
<td>236 (61.0%)</td>
</tr>
<tr>
<td>South-East Asian</td>
<td>97 (19.4%)</td>
<td>21 (28.0%)</td>
<td>34 (8.8%)</td>
</tr>
<tr>
<td>South Asian</td>
<td>90 (18.0%)</td>
<td>15 (20.0%)</td>
<td>84 (21.7%)</td>
</tr>
<tr>
<td><strong>Maternal outcomes information</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational hypertension</td>
<td>20 (3.9%)</td>
<td>5 (6.7%)</td>
<td>31 (7.9%)</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>11 (2.2%)</td>
<td>2 (2.7%)</td>
<td>17 (4.3%)</td>
</tr>
<tr>
<td>Preterm delivery</td>
<td>54 (10.6%)</td>
<td>5 (6.7%)</td>
<td>23 (5.9%)</td>
</tr>
<tr>
<td>Spontaneous onset of labour</td>
<td>305 (59.9%)</td>
<td>48 (64.0%)</td>
<td>78 (20.0%)</td>
</tr>
<tr>
<td>Induced onset of labour</td>
<td>118 (23.2%)</td>
<td>17 (22.7%)</td>
<td>218 (55.9%)</td>
</tr>
<tr>
<td>------------------------</td>
<td>-------------</td>
<td>------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Elective CS</td>
<td>72 (14.1%)</td>
<td>8 (10.7%)</td>
<td>87 (22.3%)</td>
</tr>
<tr>
<td>Emergency CS</td>
<td>85 (16.7%)</td>
<td>16 (21.3%)</td>
<td>73 (18.7%)</td>
</tr>
<tr>
<td>Instrumental delivery</td>
<td>78 (12.8%)</td>
<td>17 (22.7%)</td>
<td>50 (15.3%)</td>
</tr>
<tr>
<td>Shoulder dystocia</td>
<td>8 (1.6%)</td>
<td>2 (2.7%)</td>
<td>5 (1.3%)</td>
</tr>
<tr>
<td>Neonatal outcome information</td>
<td>Customized LGA</td>
<td>31 (6.1%)</td>
<td>3 (4.0%)</td>
</tr>
<tr>
<td></td>
<td>Customized SGA</td>
<td>63 (12.4%)</td>
<td>16 (21.3%)</td>
</tr>
<tr>
<td></td>
<td>Obesity</td>
<td>170 (33.5%)</td>
<td>29 (39.2%)</td>
</tr>
<tr>
<td></td>
<td>Leanness</td>
<td>18 (3.5%)</td>
<td>2 (2.7%)</td>
</tr>
<tr>
<td></td>
<td>Hypoglycaemia</td>
<td>31 (6.1%)</td>
<td>3 (4.0%)</td>
</tr>
<tr>
<td></td>
<td>Jaundice</td>
<td>45 (8.8%)</td>
<td>8 (10.7%)</td>
</tr>
<tr>
<td></td>
<td>Respiratory distress</td>
<td>32 (6.3%)</td>
<td>5 (6.7%)</td>
</tr>
<tr>
<td></td>
<td>NICU/SCN admission</td>
<td>85 (16.7%)</td>
<td>8 (10.7%)</td>
</tr>
</tbody>
</table>
Appendix 6 List of flowchart, tables and charts

1. Flowchart

Flowchart 1 - IADPSG diagnostic procedures of GDM

Flowchart 2 – The public stratification system for GDM management in ACT health Diabetes service

Flowchart 3 - Study Population

2. Table

Table 1 - Recommendations for screening procedures and diagnostic criteria for GDM

Table 2 - Screening and diagnosis of GDM in this research

Table 3 - Institute of Medicine Recommendations for total weight gain and rate of weight gain during pregnancy, by pre-pregnancy BMI

Table 4 - Data collection from the medical record system

Table 5 - Maternal age, BMI, gestational age at first appointment, gestational age when GDM was diagnosed, number of gestations and parity
Table 6 - Prevalence of cases with missing data on maternal age, BMI, gestational age at first appointment, gestational at when GDM was diagnosed, number of gestations and parity.

Table 7 - Prevalence of cases with missing data regarding GDM history and Family History of Diabetes

Table 8 - Missing data on smoking status and alcohol consumption

Table 9 - Missing data on maternal ethnicity.

Table 10 - GCT and OGTT results.

Table 11 - Missing data of GCT and OGTT results.

Table 12 - Missing data of perineal status and sutured status.

Table 13 - Information regarding after delivery hospital staying and after delivery bleeding

Table 14 - Missing data of after delivery information

Table 15 - Information regarding birth weight, birth length and Ponderal Index.

Table 16 - Missing data for birth weight, length, PI, macrosomia, low birth weight, obesity, leanness, LGA, SGA.

Table 17 - Missing data of NICU/SCN staying time and admission reasons.

Table 18 - NICU admissions of neonates born in The Canberra Hospital.

Table 19 - Maternal demographic information for three groups part I.
Table 20 - Maternal demographic information for three groups Part II.

Table 21 - Missing data in demographic data.

Table 22 - Results of HbA1c, TSH and Vitamin D.

Table 23 - Missing data of HbA1c tests, TSH tests, and Vitamin D levels.

Table 24 - Maternal outcomes for three groups.

Table 25 - Neonatal outcomes of three groups.

3. Chart

Chart 1 - Maternal glucose concentration associated with adverse perinatal outcomes

Chart 2 - History of GDM and family history of diabetes

Chart 3 - Smoking status and alcohol consumption during pregnancy.

Chart 4 - Maternal Ethnicity

Chart 5 - Maternal pre-existing complications.

Chart 6 - Pregnancy-induced hypertension

Chart 7 - The onset of preterm birth

Chart 8 - Onset of labour.

Chart 9 - Mode of delivery

Chart 10 - Methods of birth.
Chart 11 - Reasons for elective CS

Chart 12 - Reasons for emergency CS.

Chart 13 - Perineal statuses.

Chart 14 - Delivery complications including shoulder dystocia and meconium liquor

Chart 15 - Proportions of three groups of Apgar score at 1 minute

Chart 16 - Proportion of three groups of Apgar score at 5 minute.

Chart 17 - Information regarding macrosomia, low birth weight, neonatal obese, and neonatal underweight.

Chart 18 - Prevalence of cLGA and cSGA babies.

Chart 19 - Information regarding hypoglycaemia, jaundice, respiratory distress, NICU/SCN admission

Chart 20 - Reasons for NICU/SCN admissions.

Chart 21 - Information regarding neonatal hypoglycaemia and treatment.

Chart 22 - Information regarding neonatal jaundice and treatment.

Chart 23 - Respiratory distress and causes.

Chart 24 - The treatment options of respiratory distress.

Chart 25 - Other main complications.
Reference


6. Bennewitz HG. The first recorded case of diabetic pregnancy University of Berlin1824.


475. Feely J, Isles TE. Screening for thyroid dysfunction in diabetics1979 1979-12-01 08:00:00. 1439-p.


511. Shin D, Song WO. Prepregnancy body mass index is an independent risk factor for gestational hypertension, gestational diabetes, preterm labor, and small- and large-


527. Whitworth M, Quenby S, Cockerill RO, Dowswell T. Specialised antenatal clinics for women with a pregnancy at high risk of preterm birth (excluding multiple pregnancy) to improve maternal and infant outcomes. The Cochrane database of systematic reviews. 2011(9):CD006760-CD.
