The Importance of a Continuum of Care Before, During and After Pregnancy in Women with Type 1 and Type 2 Diabetes along the Irish Atlantic Seaboard

A thesis submitted for degree of Doctor of Philosophy to the School of Medicine, College of Medicine, Nursing and Health Sciences, National University of Ireland Galway.

By

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Summary of Contents

Pregestational diabetes is the most common chronic medical condition to complicate pregnancy and is associated with an increased risk of morbidity and mortality for the mother-offspring pair. Optimising outcomes for this population is an important public health issue and requires the identification of modifiable determinants of risk and the provision of high quality clinical care. My thesis addresses the importance of a continuum of care before, during and after pregnancy for women with type 1 and type 2 diabetes.

In this thesis, I firstly report pregnancy outcomes for a regional cohort of women with pregestational diabetes in the West of Ireland over a decade, and examine in detail the issues of gestational weight gain (GWG) and diabetic retinopathy. Employing a number of different methodological and statistical approaches, I outline the clinical and economic benefits of a regional approach to prepregnancy care for women with diabetes. Next, I describe a protocol for developing a core outcome set (COS) for studies evaluating prepregnancy care for women with pregestational diabetes, and report the study results and the final COS. Finally, I examine women at 12 months post-partum to assess the impact of pregnancy and prepregnancy care on longer-term treatment goals in women with diabetes.

The work of this thesis enhances existing knowledge on the subject of pregestational diabetes. It provides up-to-date, regional data on pregnancy outcomes and identifies excessive GWG as an independent risk factor for adverse outcomes. This is the first piece of work to outline both the clinical and economic benefits of a regional prepregnancy care programme. The thesis identifies a need for a paradigm change in the way post-partum care is delivered to women with diabetes. A COS for studies evaluating prepregnancy care is now available and it is anticipated that it will stimulate further high-quality research in this area.

Declaration

This thesis is submitted to the National University of Ireland, Galway in accordance with the requirements for Doctor of Philosophy (PhD) in the School of Medicine, Faculty of Health Sciences.

This thesis is a record of my own work and has not been submitted for any other academic award in this university or in any other academic institution.

Parts of this article-based thesis have appeared in peer reviewed publications and presentations. All information sources are fully referenced.

I have no conflict of interest pertaining to the subject matter of this work

Aoife Egan

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Dedication

This thesis is dedicated to Sadhbh.

Published Papers and Outputs Arising from this Work

Published Papers

Egan AM, Dunne FP
Pre-pregnancy care for women with diabetes mellitus.
British Journal of Hospital Medicine, 2016; 77 (12): c191 - c193

Owens LA, Egan AM, Carmody L, Dunne F.
Ten years of optimizing outcomes for women with type 1 and type 2 diabetes in prengnacy – the Atlantic DIP experience.
Journal of Clinical Endocrinology and Metabolism, 2016; 101 (4): 1598 – 605

Egan AM, Danyliv A, Carmody L, Kirwan B, Dunne FP
A prepregnancy care program for women with diabetes: effective and cost saving.
Journal of Clinical Endocrinology and Metabolism, 2016; 101 (4): 1807-15

Egan AM, Smith V, Devane D, Dunne FP
Effectiveness of prepregnancy care for women with pregestational diabetes mellitus: protocol for a systematic review of the literature and identification of a core outcomes set using a Delphi survey.
Trials. 2015; 16(1): 356.

Egan AM, Murphy HR, Dunne FP
The management of type 1 and type 2 diabetes in pregnancy.
Quarterly Journal of Medicine, 2015; 108 (12): 923-7

Egan AM, McVicker L, Heerey A, Carmody L, Harney F, Dunne FP
Diabetic Retinopathy in Pregnancy: A Population-Based Study of Women with Pregestational Diabetes
Journal of Diabetes Research, 2015; 2015: 310239

Egan AM, Dennedy MC, Al-Ramli W, Heerey A, Avalos G, Dunne F
ATLANTIC-DIP: Excessive Gestational Weight Gain and Pregnancy Outcomes in Women With Gestational or Pregestational Diabetes Mellitus.
Journal of Clinical Endocrinology and Metababolism. 2014; 99 (1): 212-9.

Egan AM, Carmody L, Kirwan B, Dunne FP.
Care of Women with Diabetes Before, During and After Pregnancy – Time for New Approach?

Diabetic Medicine. 2017 doi: 10.1111/dme.13342 [epub ahead of print]

Paper In Press

Egan AM, Galjaard S, Maresh M, Loeken MR, Napoli A, Anastasiou E, Noctor E, De Valk H, Van Poppel M, Todd M, Smith V, Devane D, Dunne FP.
A Core outcome set for studies evaluating the effectiveness of prepregnancy care for women with pregestational diabetes.
Diabetologia March 2017

Book Chapter

Egan AM and Dunne FP.
Excessive gestational weight gain and pregnancy outcomes in gestational and pre-gestational diabetes.
Nutrition and Diet in Maternal Diabetes 2016, Springer. [in print]

Oral Communications at National / International Meetings

8th West of Ireland Integrated Diabetes care Conference, 16th – 17th October 2015, Galway, Ireland
An update on diabetes in pregnancy
Egan AM

51st EASD Annual Meeting, 15th–18th September 2015, Stockholm, Sweden
Prepregnancy care for a region: exploring the clinical and economic effects.
Egan AM, Danyliv A, Carmody L, Dunne FP

50th EASD Annual Meeting, 16th -19th September 2014, Vienna, Austria
Screening for diabetic retinopathy in pregnancy.
Egan AM, McVicker L, Heerey A, Carmody L, Harney F, Dunne FP

Irish Endocrine Society, 38th Annual Meeting, 8th November 2013, Kilkenny.
ATLANTIC DIP: Excessive gestational weight gain and pregnancy outcomes in women with gestational or pre-gestational diabetes mellitus.
Egan AM, Dennedy MC, Al-Ramli W, Heerey A, Avalos G, Dunne F.

45th Annual Diabetic Pregnancy Study Group meeting, 3rd October 2013, Malta.
Does weight gain matter in diabetic pregnancy?
Egan AM, Dennedy MC, Al-Ramli W, Heerey A, Dunne F

Poster Presentations at National / International Meetings

Irish Endocrine Society 40th Annual Meeting, 14th – 15th October 2016, Belfast, Northern Ireland
Atlantic DIP: Pregnancy and Beyond – An Evaluation of Women with Diabetes One Year Post Delivery
Egan AM, Carmody L, Kirwan B, Dunne FP

76th Scientific Sessions of the American Diabetes Association, June 10th – 14th 2016, New Orleans, USA
Atlantic DIP: An evaluation of women with type 1 and type 2 diabetes at 12 months postpartum
Egan AM, Carmody L, Kirwan B, Dunne FP

European Diabetes Epidemiology Group Meeting 2016, 16th – 18th April, Kildare, Ireland
Atlantic DIP: Pregnancy and Beyond – An Evaluation of Women with Diabetes One Year Post Delivery
Egan AM, Carmody L, Kirwan B, Dunne FP

47th Annual Diabetic Pregnancy Study Group Meeting, 1st – 4th October 2015, Malaga, Spain
Prepregnancy care for a region: exploring the clinical and economic effects.
Egan AM, Danyliv A, Carmody L, Dunne FP

ENDO 2015, March 4th – 8th 2015, San Diego, California, USA
A Regional Prepregnancy Care Program for Women with Pregestational Diabetes: Is it Worthwhile?
Egan AM, Danyliv A, Carmody L, Dunne FP

46th Annual Diabetic Pregnancy Study Group Meeting, 2nd – 4th October 2014, Budapest, Hungary
Screening for diabetic retinopathy in pregnancy
Egan AM, McVicker L, Heerey A, Carmody L, Harney F, Dunne FP

49th EASD Annual Meeting, 23rd September 2013, Barcelona, Spain.
ATLANTIC DIP: gestational weight gain and pregnancy outcomes in women with pregestational and gestational diabetes mellitus
Egan AM, Dennedy MC, Al-Ramli W, Heerey A, Dunne F

73rd Scientific Sessions of the American Diabetes Association, 21st June 2013, Chicago, USA
ATLANTIC DIP: Gestational Weight Gain and Pregnancy Outcomes in women with Pre-Gestational Diabetes Mellitus
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A new website for women with diabetes in pregnancy:
www.atlanticdipireland.com (January 2016)

A national seminar for women with diabetes (Galway, Ireland, March 2016)

A stakeholder meeting to involve healthcare professionals and women with diabetes. The aim of the meeting was to facilitate development and publication of a core outcome set for prepregnancy care programmes for women with diabetes (Dublin, Ireland, October 2016)

A diet book for women with diabetes (December 2016)

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List of Abbreviations

ACE	Angiotensin Converting Enzyme
ADA	American Diabetes Association
BMI	Body Mass Index
CEMACH	Confidential Enquiry into Maternal and Child Health
CI	Confidence Intervals
COMET	Core Outcome Measures in Effectiveness Trials
CONCEPTT	Continuous Glucose Monitoring in Women with Type 1 Diabetes in Pregnancy
COS	Core Outcome Set
COS-STAR	Core Outcome Set – STAndards for Reporting
CPI	Consumer Price Index
CROWN	CoRe Outcomes in WomeN's Health
CSII	Continuous Subcutaneous Insulin Infusion
DCCT	Diabetes Control and Complications Trial
DI	Diabetes Ireland
DIP	Diabetes in Pregnancy
Diabetes	Diabetes Mellitus
DPSG	Diabetic Pregnancy Study Group
DRG	Diagnosis Related Group
EASD	European Association for the Study of Diabetes
EBCOG	European Board and College of Obstetrics and Gynaecology
EMERGE	Effectiveness of MEtformin in addition to usual care in the Reduction of GEstational diabetes mellitus
EUROCAT	European Surveillance of Congenital Anomalies
FIGO	International Federation of Gynecology and Obstetrics

GDM	Gestational Diabetes Mellitus
GLM	Generalised linear regressions
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GWG	Gestational Weight Gain
HbA1c	Glycated Haemoglobin
HIV	Human Immunodeficiency Virus
HRB	Health Research Board
HSE	Health Service Executive
IADPSG	International Association of Diabetes and Pregnancy Study Groups
IES	Irish Endocrine Society
IFCC	International Federation of Clinical Chemistry
INDI	Irish Nutrition and Dietetic Institute
IOM	Institute of Medicine
IRMA	Intraretinal Microvascular Abnormality
LGA	Large for Gestational Age
MDI	Multiple Daily Injection
MiTy	Metformin in women with Type 2 diabetes in pregnancy
mmHg	Millimetres of Mercury
MODY	Maturity Onset Diabetes of the Young
NICE	National Institute for Health and Care Excellence
NICU	Neonatal Intensive Care Unit
NPID	National Pregnancy In Diabetes
NVD	New Vessels on Disc
NVE	New Vessels Elsewhere

OR	Odds Ratios
OGTT	Oral Glucose Tolerance Test
SAG	Study Advisory Group
SGA	Small for Gestational Age
SPSS	Statistical Package for the Social Sciences
SD	Standard Deviation
WHO	World Health Organization
≤	Less than or equal to
≥	Greater than or equal to
<	Less than
>	Greater than
±	Plus or minus

Chapter 1: Introduction

The management of type 1 and type 2 diabetes in pregnancy. Egan AM, Murphy HR, Dunne FP. QJM. 2015 Dec;108(12):923-7.
(Reproduced with Permission - Appendix 1)

1.1 Diabetes Mellitus: Definition and Diagnosis

1.1.1 Brief History of Diabetes Mellitus

In the 1st century Aretus the Cappadocian (81-133) produced the first clear written description of the condition now known as diabetes mellitus (diabetes), referring to it as 'diabainein', meaning 'a siphon'[1-4]. This term alluded to the polyuria associated with the condition. In 1675, the British physician Thomas Willis (1621 – 1675) added the Greek word 'mellitus' which means 'like honey'[5]. This was included to reflect the sweet smell and taste of the patients' urine. Many years later in 1889 in Austria, Joseph Von Mering (1849-1908) and Oskar Minkowski (1858-1931) discovered the role of the pancreas in the pathogenesis of diabetes[6]. This work paved the way for a series of experiments by Frederick Banting (1891-1941) and Charles Best (1899-1978) who isolated insulin in Canada in 1921 and launched a new era in diabetes treatment[7-9].

1.1.2 Modern Understanding of Diabetes

Nowadays, diabetes represents a series of metabolic conditions associated with hyperglycaemia and caused by defects in insulin secretion, sometimes exacerbated by defects in insulin action[10,11]. Acute manifestations of hyperglycaemia include polyuria, polydipsia, weight loss, sometimes with polyphagia and blurred vision[10]. In the setting of absolute or relative insulin deficiency diabetic ketoacidosis may occur[12]. The chronic hyperglycaemia of diabetes is associated with long-term damage, dysfunction and failure of various organs. Features of chronic hyperglycaemia include microvascular complications affecting the retina, kidney or peripheral nerves and macrovascular complications including myocardial infarction, stroke and peripheral arterial disease[13-17].

1.1.3 Categories of Diabetes

There are four major categories of diabetes. These are type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes mellitus (GDM) and other specific types of diabetes mellitus[18].

(i) In type 1 diabetes mellitus, pancreatic beta-cells are destroyed and this typically leads to absolute insulin deficiency[19]. Type 1 diabetes is frequently associated with autoimmunity.

(ii) Type 2 diabetes mellitus is a complex metabolic disorder associated with beta-cell dysfunction and varying degrees of insulin resistance[20].

(iii) GDM is defined as diabetes occurring in pregnancy that is not clearly overt diabetes[18,21]. It is a common medical complication of pregnancy associated with an increase in adverse pregnancy outcomes and a lifelong elevated risk of type 2 diabetes[22-26].

(iv) Other specific types of diabetes mellitus, for each of which the underlying defect or disease process can be identified form the final category. The most common of these is maturity-onset diabetes of the young (MODY), a familial form of diabetes inherited in an autosomal dominant manner and associated with mutations in certain beta-cell or hepatic genes (e.g. glucokinase)[27]. Other well-characterized forms of diabetes include mitochondrial diabetes, diabetes associated with pancreatic disease (e.g. haemochromatosis-related diabetes) and with corticosteroid (or other) hormone excess. Diabetes may be iatrogenic with certain drugs frequently implicated (e.g. protease inhibitors in human immunodeficiency virus (HIV) infection, atypical antipsychotics in schizophrenia)[10,11].

1.1.4 Diagnosis of Diabetes

The diagnosis of diabetes, may be made in any one of the following scenarios[10,28]:

(i) Random plasma glucose concentration ≥11.1 mmol/L in the presence of classical symptoms of hyperglycaemia (polydipsia, polyuria, weight loss).

(ii) Fasting plasma glucose ≥7.0 mmol/L. Fasting is defined as no caloric intake for at least 8 hours.

(iii) Plasma glucose ≥11.1 mmol/L 2 hours after a glucose load

containing the equivalent of 75 g anhydrous glucose dissolved in water (i.e. the oral glucose tolerance test; OGTT).

(iv) Glycated haemoglobin (HbA1c) ≥48 mmol/mol (6.5%).

It should be noted that, in the absence of symptoms, diagnosis should not be based on a single glucose determination but requires confirmatory testing[10]. The above diagnostic criteria based on plasma glucose concentration were established initially by an expert committee of the American Diabetes Association (ADA) in 1997 and later ratified by the World Health Organization (WHO)[29,30]. The diagnostic cut-off points of 7.0 mmol/L (fasting) and 11.1 mmol/L (OGTT 2-hour value) are based on the concentrations at which retinopathy begins to appear in a population[30,31].

The use of HbA1c as a diagnostic tool for diabetes reflects a recent change in practice, recommended by an International Expert Committee in July 2009[28]. HbA1c provides an integrated measure of prevailing plasma glucose over the previous 8-12 weeks[32]. Although it is the mainstay of monitoring glycaemic control among individuals with established diabetes, it had not previously been used to diagnose the condition[33]. This is mainly because assays used to measure HbA1c were not standardized around the world. Standardization of assays has now been achieved in the United States with all assays reporting results aligned with the HbA1c assay used in the Diabetes Control and Complications Trial (DCCT). In other parts of the world the International Federation of Clinical Chemistry (IFCC) recommendation, that the reporting of HbA1c results be changed to a more robust clinical chemistry standard (expressed in mmol/mol) and not a DCCT-aligned result (expressed in %), has been implemented[11,34,35].

In 2010, the ADA officially recommended HbA1c testing for the diagnosis of diabetes and in 2011 the WHO endorsed this recommendation[36,37]. This endorsement was made on the basis that stringent quality assurance tests are in place, assays are standardized and there are no conditions present that preclude accurate measurement of the HbA1c. The most common factors

affecting HbA1c are haemoglobinopathies, certain anaemias, and disorders associated with accelerated red cell turnover such as malaria[38,39]. Other situations in which HbA1c is not appropriate for diagnosis include those in which diabetes may have been present for less than 2 months. This may be suggested by the presence of symptoms for fewer than 2 months, by prescription within the past 2 months of diabetogenic medication, or in the context of acute pancreatic damage. Finally, HbA1c is not suitable for the diagnosis of GDM[38,39].

The ADA recommend that, when feasible, and in the absence of symptoms, the same test be repeated for confirmation. However, if a patient has discordant results on two different tests, the test that has produced a result above the diagnostic cut point should be repeated and the diagnosis made on the basis of the outcome[18].

1.1.5 Diagnosis of Gestational Diabetes Mellitus

The diagnosis of GDM is controversial and screening and diagnostic criteria are inconsistent across Europe and indeed worldwide[40]. Some groups advocate universal screening using either a diagnostic OGTT or a glucose challenge test, whereas others recommend risk factor based screening[41-43]. The amount of glucose recommended for the OGTT also differs (75g or 100g), and there is significant variation in postprandial glucose concentrations above which GDM is diagnosed[21,41-44]. The WHO, The Endocrine Society and the International Federation of Gynecology and Obstetrics (FIGO) all endorse the 2008 International Association of Diabetes and Pregnancy Study Groups (IADPSG) 2008 criteria (ie. fasting glucose ≥5.1 mmol/L, 1-hour post-prandial ≥10.0 mmol/L or 2-hour post-prandial ≥8.5 mmol/L after 75g OGTT)[21,45,46]. This is considered a 'one-step' approach to diagnosis. The ADA endorses this approach but state that a 'two-step' approach is also acceptable. This involves a 50-g glucose challenge (non-fasting) followed by a 100g OGTT for those who screen positive (ie. glucose ≥7.8 mmol/L)[43]. The diagnosis of GDM is then made if at least 2 out of 4 glucose levels are met or exceeded on the OGTT. The Carpenter/Coustan (fasting glucose 5.3 mmol/L, 1 hour 10.0 mmol/L, 2

hour 8.6 mmol/L, 3 hour 7.7 mmol/L)[47] or National Diabetes Data Group (fasting 5.8 mmol/L, 1 hour 10.6 mmol/L, 2 hour 9.2 mmol/L, 3 hour 8.0 mmol/L) criteria may be used[48]. National Institute for Health and Care Excellence (NICE) Guidelines in the United Kingdom advise a diagnosis of GDM if the woman has either a fasting glucose of ≥5.6 mmol/L or a 2-hour glucose level of ≥7.8 mmol/L after a 75g glucose load[42].

1.1.6 Classification of Diabetes

Correct classification of an individuals' diabetes is important and is typically based on history and clinical examination[49]. Further investigation is required where uncertainty surrounds the diagnosis. These investigations may include the measurement of diabetes-specific autoantibody titers to confirm autoimmune diabetes or genetic testing to identify monogenic diabetes[18,49]. Such evaluation is patient-specific and based on the judgment of health care professional.

1.2 Pregestational Diabetes and Pregnancy: Epidemiology and Pathophysiology

Diabetes is the most common chronic medical condition in the pregnant population and while pregnancy is typically a joyous event, it can pose significant risk to the mother and infant in the setting of diabetes[50]. Although the exact prevalence is unclear in Ireland, data from England and Wales reveal that up to 5% of the 700,000 women who give birth each year have diabetes[42]. It is further estimated that in this population of women with diabetes during pregnancy, approximately 87.5% have GDM, 7.5% have type 1 diabetes and 5% have type 2 diabetes[42]. This thesis will focus on pregnancy in the setting of type 1 and type 2 diabetes, also referred to as pregestational diabetes.

During normal pregnancy, there are significant alterations to glucose metabolism. Glucose, the primary energy source used by the foetus, transfers from mother to foetus via the GLUT-1 transporter[51]. Fasting

glucose levels are lower than in the non-pregnant state and fasting insulin levels are also reduced, a combination that leads to the state of accelerated ketosis seen during periods of fasting[52]. In later pregnancy, a progressive rise in postprandial glucose and its associated insulin response, associated with decreased insulin sensitivity, parallels the growth of the foetal placental unit ensuring adequate nutrients for the developing foetus. In the setting of type 1 and type 2 diabetes, there exists absolute and relative deficiency of insulin respectively and this prevents this normal adaptive process. Women with type 1 diabetes require increasing insulin doses and those with type 2 diabetes will typically require insulin treatment[51].

The hyperglycaemic-hyperinsulinemia hypothesis, also known as the Pederson hypothesis was described by the Danish epidemiologist Jorgen Pedersen (1914-1978) in the 1950s [53,54]. The theory aims to explain the underlying pathology that leads to the disordered foetal development associated with pregnancy affected by diabetes. It states that *'maternal hyperglycaemia results in foetal hyperglycaemia and, hence, in hypertrophy of foetal islet tissue with insulin-hypersecretion. This again means a greater foetal utilisation of glucose'*[54,55]. In simpler terms, this hypothesis describes increased maternal glucose crossing the placenta from mother to foetus, resulting in increased foetal glucose concentrations and insulin response. More recently, it is suggested that additional factors such as alterations in lipid metabolism and inflammatory change may contribute to the abnormal metabolic environment associated with diabetic pregnancies, particularly when obesity co-exists[53]. Such metabolic disruptions can affect organogenesis in early pregnancy, and as the pregnancy progresses, this abnormal intrauterine environment may result in excessive foetal growth with resultant macrosomia and associated adverse clinical outcomes [56-58].

For the woman with diabetes, there are additional concerns during pregnancy, particularly in the presence of established diabetes complications. Diabetic retinopathy, for example, may deteriorate during pregnancy[59,60]. While the pathogenic mechanisms are not fully understood, factors such as hyperglycaemia and physiological changes associated with

pregnancy itself including hypervolaemia, hypercoagulation and impaired retinal autoregulation all play a role[61]. The presence of diabetic nephropathy is associated with the development of severe maternal hypertension which can ultimately necessitate interruption of the pregnancy, and impaired placental development which may result in foetal growth restriction and risk of stillbirth[62].

1.3 Pregestational Diabetes and Pregnancy: Review of Clinical outcomes

Many studies reveal poor clinical outcomes for women with pregestational diabetes in pregnancy. In Ireland, the Atlantic Diabetes in Pregnancy (DIP) initiative completed a prospective evaluation of pregnancy outcomes in pregestational diabetes along the Irish Atlantic Seaboard from 2006 – 2007 (n=104 pregnancies). They found a stillbirth rate 5 times, perinatal mortality rate 3.5 times and congenital malformation rate 2 times that of the background population. A total of 28% women had received prepregnancy care and 43% received folic acid preconceptually[58]. In 2006, Macintosh et al described outcomes for women with type 1 and type 2 diabetes attending 231 maternity units in England, Wales and Northern Ireland (n=2359 pregnancies). Perinatal mortality was comparable in women with type 1 and type 2 diabetes and was nearly 4 times the background population. The congenital anomaly rate was more than double the background population with neural tube defects and congenital heart defects most commonly observed[57]. The 2015 National Pregnancy in Diabetes (NPID) audit in the United Kingdom revealed some improvements. It reported a stillbirth rate of 10.7/1,000 live and stillbirths for women with type 1 diabetes and 10.5/1,000 for women with type 2 diabetes compared to 4.7/1,000 in the general population[63]. Foetal macrosomia as described previously (chapter 1, 1.3) is associated with many adverse pregnancy outcomes including the need for operative delivery, shoulder dystocia, neonatal hypoglycaemia and stillbirth, and continues to affect approximately 50% infants born to women with pregestational diabetes[57,64-66].

An emerging challenge in this field is the increasing prevalence of type 2 diabetes in pregnancy associated with the concurrent rise in obesity. These women are more commonly from ethnic minorities and although predominantly cared for in community settings with minimal access to specialist care, they experience similar adverse outcomes to those with type 1 diabetes and are a particularly vulnerable group[65,67]. Finally, it is becoming increasingly evident that exposure to maternal diabetes in utero may also have a longer term negative impact on the offspring, with one recent study noting that adolescent offspring of women with type 1 diabetes have lower cognitive function compared with a control group even after adjusting for confounding variables[68]. In addition, long term follow up of offspring of women with diabetes reveal that they have elevated rates of obesity and type 2 diabetes later in life[69].

Overall we have not achieved the target of the Saint Vincent declaration which in 1989 called for outcomes equal to that of the non-diabetic pregnancy within 5 years[70]. However, on a more positive note, structured clinical care programmes providing coordinated, evidence-based care to these women before and during pregnancy have demonstrated improved clinical outcomes[67,71].

Sections 1.4 - 1.6 of this thesis will draw on published literature, national and international guidelines to discuss concepts considered key to the optimal management of women with pregestational diabetes[42-45].

1.4 Prepregnancy Care for Women with Pregestational Diabetes: What does the Literature Show?

The risk of certain adverse outcomes including malformations and perinatal mortality is related to poor glycaemic control in early pregnancy[72]. Intervention before the pregnancy is therefore necessary to ensure optimal glycaemic control throughout the time of conception and this critical early

stage. The value of a 'prepregnancy' clinic was first demonstrated almost 30 years ago and it is now accepted practice that preconception counselling is provided to all women with diabetes who are considering pregnancy[45,73]. In order to facilitate this process, the possibility of pregnancy should be identified, by direct questioning, at each consultation, in all women of child-bearing age with diabetes[44].

Typically women attending a centre for prepregnancy care are reviewed at 1-3 monthly intervals. The importance of avoiding an unplanned pregnancy should be explained and contraception advised until treatment goals are achieved. A full medication review should take place and any medications unsuitable for pregnancy such as angiotensin converting enzyme (ACE) inhibitors or statins should be discontinued[67]. With the exception of metformin, all hypoglycaemic agents should be discontinued. If necessary, smoking and alcohol cessation advice should be provided. Retinal evaluation should take place and if therapy is required, pregnancy deferred until its completion. Satisfactory blood pressure control is necessary [<130/80 millimetres of mercury (mmHg)] and if there is evidence of renal dysfunction, nephrology review is recommended[45]. Thyroid status must be assessed and managed at this time. Hypothyroidism may reduce fertility, increase the risk of miscarriage and impair foetal brain development if untreated[45]. All women require a dietician review and those with a body mass index (BMI) above 27kg/m^2 should be offered advice on how to lose weight. Prior to discontinuing contraception, folic acid 5mg once daily is advised until 12 weeks gestation[42]. Although there is no evidence of a clinical benefit for this higher dose, several advisory groups have made this recommendation based on a theoretical benefit in reducing the increased risk of neural tube defects associated with diabetes mellitus in pregnancy[42,45,57].

Women on insulin should be treated with a multiple daily injection (MDI) regimen or continuous subcutaneous insulin infusion (CSII) in preference to split-dose, premixed insulin[45]. The rapid-acting insulin analogues aspart and lispro are safe, licenced and commonly used in pregnancy[42,74]. Safety data are largely available from observational studies, but a randomised controlled

trial of insulin aspart versus regular soluble insulin in 322 women with type 1 diabetes showed similar efficacy with a tendency to lower rates of hypoglycaemia and without apparent toxicity[51,74,75]. Newer, long-acting analogues also appear safe for use in pregnancy and have begun to replace the traditionally used isophane insulin in clinical practice[76]. Detemir in particular, is approved for use in pregnancy and a recent study indicates that it does not cross the human placenta[51,77]. A randomised controlled trial comparing perinatal outcomes using insulin detemir or neutral protamine hagedorn in type 1 diabetes identified no safety issues in relation to detemir. In the trial, detemir was associated with lower fasting plasma glucose values in later pregnancy and similar pregnancy outcomes to neutral protamine hagedorn insulin[76,78]. Insulin glargine is also frequently used in clinical practice during pregnancy, and although no large randomised controlled trial data are available, observational studies do not reveal any concerning adverse outcomes[79,80].

Regular capillary blood glucose monitoring must take place and both pre- and postprandial levels are required. The 2015 NICE guidelines advise women with diabetes who are planning to become pregnant to maintain their HbA1c below 48mmol/mol (6.5%) as this is associated with a reduction in congenital anomalies to close to that seen in the background population[42]. The major limitation to tight glycaemic targets is hypoglycaemia and instruction on its management including use of glucagon should be provided to the patient and/or family members. Women with type 1 diabetes should have the ability to test for ketones (urinary or capillary) should they become unwell or hyperglycaemic.

Attendance at prepregnancy care is associated with a reduction in congenital anomalies, perinatal mortality and maternal HbA1c in the 1st trimester of pregnancy[81]. These reductions are applicable to women with both type 1 and type 2 diabetes. Unfortunately, attendance at prepregnancy care is not universal and therein lies a challenge in getting advice to those who need it in an acceptable and understandable form. Of concern is the Confidential Enquiry into Maternal and Child Health (CEMACH) survey which revealed

that only 17% maternity services in the United Kingdom actually provided structured multidisciplinary preconception care[65]. The 2015 NPID audit revealed a large variation between services and localities in meeting NICE recommendations for pregnancy preparation and overall, subjects were not well prepared for pregnancy. Specifically the report revealed that just 46% of women with type 1 diabetes and 23% of women with type 2 diabetes were taking the recommended 5mg folic acid prior to pregnancy, and the majority of women did not have contact with the antenatal diabetes team before they were 8 weeks pregnant[63]. Murphy et al demonstrated that a regionalised approach to preconception counselling and prepregnancy care improved pregnancy preparation and reduced the risk of adverse pregnancy outcomes, however women with type 1 diabetes were still more likely to have had documented preconception counselling (54% versus 32% with type 2 diabetes). Despite improved counselling only 27% women attended prepregnancy care clinics with significantly more women with type 1 diabetes represented (30% versus 20%). Women who attended prepregnancy care were more likely to be white and less likely to live in a deprived area, smoke cigarettes and to be overweight or obese[67]. Although women with type 1 diabetes are more likely to have suboptimal preconception control, attendance at prepregnancy care programmes is particularly poor among women with type 2 diabetes[65,82]. Cited barriers to engaging with preconception care include negative experiences with health professionals, lack of information and work commitments[82,83].

1.5 Antenatal care for women with pregestational diabetes

When the woman becomes pregnant, immediate contact with a joint diabetes and antenatal clinic should be facilitated. This concept of a combined clinic allows the diabetes physician to be involved in a meaningful way as the pregnancy progresses[84]. While these clinics may differ in terms of structure, it is important that women are reviewed every 1-2 weeks by the diabetes team and a system for diabetes consultation (eg. telephone helpline) is available on demand. Capillary blood glucose levels

are monitored before and either 1 or 2 hours after the start of each meal, before bed and if necessary overnight. Targets must be individualised and safe, however a fasting glucose of <5.3 mmol/L and 1 hour post prandial of <7.8 mmol/L are reasonable goals. HbA1c does not reliably reflect changes in mean blood glucose in pregnancy, particularly in the 2nd and 3rd trimesters, but higher levels (HbA1c >42 - 48 mmol/mol / 6.0 - 6.5%) may still be used as marker of poor glycaemic control and a pregnancy which is at increased risk of poor outcome[85]. Hypoglycaemia is a common problem in the 1st trimester and is often associated with a diminished awareness. This is particularly the case in type 1 diabetes where early pregnancy is a time of insulin sensitivity, lower glucose levels and lower insulin requirements[43]. The situation changes by approximately 16 weeks and increasing insulin resistance requires regular uptitration of insulin to achieve euglycaemia with prepregnancy insulin doses often doubling by 30 weeks gestation[84]. Recurrent hypoglycaemia affects women with type 1 diabetes more frequently than those with type 2, likely related to the fact that women with type 1 diabetes have longer diabetes duration, more hypoglycaemia unawareness and that not all women with type 2 diabetes require insulin therapy[65]. The importance of ketone testing and hypoglycaemic management should be reemphasised during the pregnancy. If there is a suspicion or diagnosis of diabetic ketoacidosis during pregnancy, this must be treated as an emergency and the woman admitted to a critical care area with immediate specialist review[42].

Excessive weight gain during pregnancy is now established as an independent risk factor for adverse pregnancy outcomes[86]. The 2009 Institute of Medicine (IOM) recommendations may be used to advise on appropriate gestational weight gain (GWG) as per BMI at booking visit and the provision of additional support to facilitate lifestyle changes to assist adherence (table 1.1)[87]. In general, physical activity should be encouraged and while some dietary modifications are necessary to prevent large increases in blood glucose, a balanced diet is advised overall. Pregnant women with diabetes should be referred to a dietician specialising in pregnancy. Sugars and simple carbohydrates should be eliminated and

replaced with more ideal carbohydrate sources including fresh vegetables, some fruits and whole grains[88]. There is no definitive evidence for the optimal proportion of carbohydrate in the diet of women with diabetes and more research is needed into the relationship between maternal dietary intake both in terms of GWG and postprandial glucose control in these women[45]. Furthermore, there are no randomised trials evaluating the effects of a modified diet for those women with diabetic nephropathy in pregnancy.

Progression of diabetic retinopathy during pregnancy is well described in both type 1 and type 2 diabetes. Various contributing factors are identified including pre-existing retinopathy, increasing duration of diabetes and higher blood pressure in early pregnancy[89]. While associations between rapid declines in HbA1c during pregnancy and deterioration in retinopathy status have been identified, the presence of retinopathy should not be considered a contraindication to rapid optimisation of glycaemic control if necessary. Instead, identification and close monitoring of those women at high risk of deterioration is advised. NICE recommend retinal assessment by digital imaging following the 1st antenatal appointment and again at 28 weeks if the 1st assessment is normal. If any diabetic retinopathy is present, an additional retinal assessment should be performed at 16-20 weeks[42].

If unknown, renal status should be established at the booking visit. Nephrology review is necessary if serum creatinine is abnormal (120 micromol/L or more) or if total protein excretion exceeds 2g/day. Renal function is closely linked with blood pressure and the latter must be monitored closely during pregnancy. Specialist care is essential as aggressive management of hypertension often requires multiple agents and is associated with improved pregnancy outcomes[90]. Calcium channel blockers such as nifedipine are commonly used while beta-blockers such as labetalol may be used with caution. Methyldopa also has proven safety during embryogenesis and is also suitable, although it is commonly associated with maternal side effects of postural dizziness[84].

Women with diabetes in pregnancy require additional foetal monitoring. As many women with diabetes have menstrual irregularities making pregnancy dating based on last menstrual period less accurate, viability of pregnancy and gestational age should be confirmed on ultrasound scan at 7-9 weeks[42]. A four-chamber view of the foetal heart and outflow tracts must be offered at 18-20 weeks with referral to a specialist centre if necessary. Monitoring of foetal growth and amniotic fluid volume is advised every 4 weeks from 28-36 weeks. When a macrosomic foetus is diagnosed on ultrasound, a specialist decision regarding the optimal method and timing of delivery is necessary. If a woman is treated with insulin and steroids are required for foetal lung maturation, additional insulin is necessary[44]. This is typically administered intravenously and infusion rates adjusted according to the glucose level on an hourly basis. Each centre should have a clear protocol in this regard.

Labour and delivery is an exciting time for the woman and her family and it is important that clear protocols are in place in the delivery unit to ensure the process runs smoothly. Home births are not advised. Women with diabetes-related complications (particularly autonomic neuropathy) may benefit from an anaesthetic consultation in the 3rd trimester to ensure the birth plan is appropriate. Pregnant women with diabetes who have a normally grown foetus should be offered elective birth through induction of labour or by elective caesarean section (if indicated) between 37 weeks + 0 days and 38 weeks + 6 days of pregnancy[42]. The presence of pregestational diabetes alone is not an indication for caesarean delivery. As maternal hyperglycaemia during labour and delivery is associated with neonatal hypoglycaemia and foetal distress, tight glycaemic control is necessary[42,91,92]. This is traditionally achieved using intravenous insulin and dextrose infusions to maintain maternal blood glucose levels at 4-7mmol/L, although CSII is increasingly used.

All neonates born to mothers with diabetes in pregnancy require review by a neonatologist on delivery. The maternity unit must have the facility to provide advanced neonatal care on demand at all times should the need

arise[44]. Unless there is a complication, neonates should go to the postnatal ward with their mother on delivery. Feeding should take place as soon as possible after birth and at regular intervals thereafter. Blood glucose testing should be carried out routinely in babies of women with diabetes at 2-4 hours after birth to exclude neonatal hypoglycaemia. This should take place earlier if there are clinical signs of hypoglycaemia such as severe irritability or seizure-like activity. Although there is controversy regarding the operational definition of hypoglycaemia, a recent UK survey including 135 National Health Service neonatal units reported that the majority defined neonatal hypoglycaemia as <2.6mmol/L[93]. In terms of treatment thresholds, NICE guidance states that if capillary plasma glucose values are below 2.0mmol/L on two consecutive readings despite maximal support for feeding or if there are abnormal clinical signs, or if the baby will not feed orally effectively, additional measures such as intravenous dextrose or tube feeding may be necessary[42]. Other neonatal complications occurring more frequently in offspring of mothers with diabetes include respiratory distress, jaundice and hypocalcaemia. These must be managed expectantly with additional testing and transfer to the neonatal care unit as deemed clinically necessary[44].

Table 1.1: Institute of Medicine Guidelines for Gestational Weight Gain[87]

Pregestational BMI Category	BMI, (kg/m^2)	Recommended Total Weight Gain (kg)	Recommended Mean Weight Gain: Trimester 2 & 3 (kg/week)
Underweight	<18.5	12.5 – 18.0	0.51 (0.44 – 0.58)
Normal weight	18.5–24.9	11.5 – 16.0	0.42 (0.35 - 0.50)
Overweight	25.0–29.9	7.0 – 11.5	0.28 (0.23 – 0.33)
Obese	≥30.0	5.0 – 9.0	0.22 (0.17 – 0.27)

BMI: body mass index

1.6 Postpartum Care for Women with Pregestational Diabetes

Typically women revert to their prepregnancy insulin doses post delivery, however a further reduction of approximately 25% may be necessary if breastfeeding is established[94]. Breastfeeding should be encouraged when possible as it may facilitate postpartum weight loss along with its well-established nutritional and immunological benefits for the infant[95-97]. Women should be advised regarding the need to monitor glucose levels carefully while breastfeeding and additional carbohydrate snacks are often required to avoid hypoglycaemia. Metformin is deemed to be safe while breastfeeding as the amounts excreted in breast milk are minimal, however it must be noted that there is not a marketing authorisation for this indication in the United Kingdom or Ireland[42,98]. Glibenclamide (glyburide) is also used in clinical practice in the management of diabetes while lactating and while there is strong evidence for its safety, information on its excretion in breast milk is limited. This information should be explained to the mother before initiating treatment[42]. Other oral or injectable hypoglycaemic agents are contraindicated while breastfeeding. Unfortunately, breastfeeding rates are low among women with diabetes, and there is a need for breastfeeding promotion research focused specifically on this group[99].

The importance of planning further pregnancies and the use of contraception in intervening periods should be reviewed. Women with diabetes can use oral contraceptives provided there are no standard contraindications to their use. Women's choice of contraception should be based on their own preferences and risk factors[42]. Women with type 2 diabetes are less likely to receive postnatal contraceptive advice than those with type 1 and this may be due to language difficulties and perceived differences in cultural attitudes[65]. If appropriate, women should be supported to achieve inter-pregnancy weight loss in order to reduce obesity-related pregnancy complications in subsequent pregnancies. Finally, as postpartum thyroiditis is more common in women with diabetes, screening thyroid function tests should take place at 3 and 6 months postpartum[45,100].

1.7 The Atlantic Diabetes in Pregnancy Initiative

Before 2005, robust regional and/or national information was unavailable on pregnancy outcomes in women with diabetes in the Republic of Ireland [50]. With approximately 11,000 births per year, the region covered by the Saolta healthcare group [previously Health Service Executive (HSE) West] of hospitals held the potential to provide accurate data (Fig 1.1). This geographical region extends from the north-western region of Ireland (Co. Donegal) to Galway city in the south covering an area of 7338 square miles and encompassing a mixed urban-rural population of approximately 500,000 people. This area contains five antenatal centres as follows:

(i) University Hospital Galway, Galway, County Galway.
(ii) Mayo University Hospital Castlebar, County Mayo.
(iii) Portiuncla University Hospital, Ballinasloe, County Galway.
(iv) Sligo University Hospital, Sligo, County Sligo.
(v) Letterkenny University Hospital, Letterkenny, County Donegal.

It must be noted that these are all public, state run hospitals and there are no private antenatal facilities in this region.

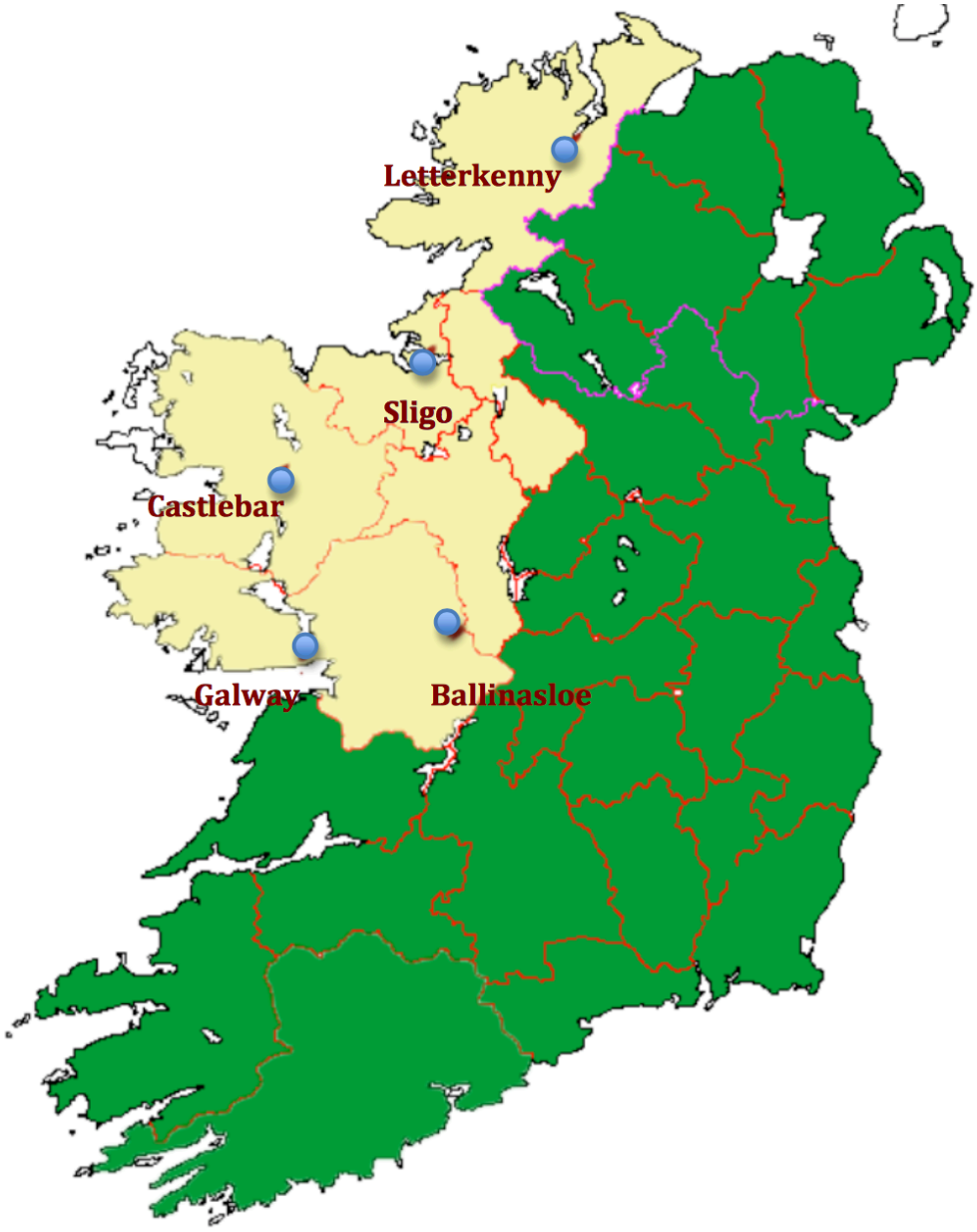
With this background information in mind, a team of healthcare professionals and academics came together and formed the Atlantic DIP initiative. Their aim was to develop a high quality clinical research programme and to use the information gleaned to provide an evidence-based service to women with diabetes in pregnancy in this region. In 2005 the Atlantic DIP team successfully sought funding in a competitive process from the Health Research Board of Ireland (HRB) for a 5-year period to investigate further this area of diabetes in pregnancy. In the area of pregestational diabetes, this included a prospective study in women with type 1 and type 1 diabetes to identify outcomes for mother and infant[58]. Subsequent HRB funding facilitated the development of a prepregnancy care programme and a prospective study to evaluate its effectiveness[101].

Overall, the Atlantic DIP initiative has resulted in the publication of more than 40 peer reviewed journal articles and led to the development of a bespoke service for women with diabetes before, during and after pregnancy in the region. This regional evidence can be extrapolated nationally and allows comparison of Irish outcomes with those of other populations. Subsequent chapters in this thesis will describe aspects of the Atlantic DIP clinical service and the associated clinical outcomes.

1.8 DIAMOND Database

One of the key aspects of the Atlantic DIP initiative was to electronically link all the antenatal centres in the network. All clinical and laboratory data obtained in the evaluation of Atlantic DIP study participants were entered in real time into a commercially available database, namely DIAMOND. This is a comprehensive diabetes management solution and is the preferred choice of many healthcare organisations in Ireland and the United Kingdom[102]. It was developed and commercialised by Hicom (Woking, United Kingdom), a company specialising in the provision software and consultancy solutions across many disciplines. DIAMOND is a Microsoft (Redmond, Washington) Access-based database, which may be accessed by institutionally authorised users only. It contains a combination of numeric and free test fields along with drop-down menu options[52]. These data are complete, accurate and easily accessible for research and audit purposes.

Figure 1.1 Map of Ireland with the region covered by the Atlantic-DIP initiative highlighted (yellow) and the 5 antenatal centres identified



1.9 Overview of Thesis Objectives

The overarching theme of this work is to study a cohort of women with pregestational diabetes in the Atlantic DIP study region. This will involve:

(i) Determining maternal and foetal pregnancy outcomes;
(ii) Evaluating a regional prepregnancy care programme;
(iii) Developing a core outcome set (COS) for studies evaluating prepregnancy care for women with diabetes; and
(iv) Evaluating these women at 12 months post-partum.

Chapter 2 will examine pregnancies in women with type 1 and type 2 diabetes and compare them across two time periods, 2005 – 2009 and 2010 – 2014. In chapter 3, the issue of GWG is examined in detail with the aim of assessing if excessive GWG is associated with an increased rate of adverse obstetric outcomes in women with pregestational diabetes. Chapter 4 describes an observational study that evaluates screening and progression of diabetic retinopathy in pregnancies complicated by pregestational diabetes.

Chapter 5 details a prospective study that involved the design, implementation and evaluation of a regional prepregnancy care programme for women with diabetes from a clinical and economic viewpoint. Chapter 6 presents a protocol for a study to develop a COS for trials and other studies evaluating the effectiveness of prepregnancy care for women with pregestational diabetes mellitus. This involves a systematic review, Delphi study and a consensus meeting. In chapter 7 the results of this study and the final COS are presented.

In chapter 8, the impact of pregnancy and prepregnancy care on longer-term treatment goals in women with diabetes is examined. In this study women with type 1 and type 2 diabetes are evaluated before, during and 12 months after pregnancy.

Chapter 2: Clinical Outcomes for Women with Type 1 and Type 2 Diabetes in Pregnancy

Ten Years of Optimizing Outcomes for Women With Type 1 and Type 2 Diabetes in Pregnancy-The Atlantic DIP Experience.
Owens LA, Egan AM, Carmody L, Dunne F.
J Clin Endocrinol Metab. 2016 Apr;101(4):1598-605.
(Reproduced with Permission – Appendix 2)

2.1 Introduction

Specialist centers worldwide strive to optimize care of women with established diabetes before and during pregnancy to minimize the risk of a poor pregnancy outcome. There is good evidence that certain interventions may reduce this risk. These include: prepregnancy care[67,81,103-109], prepregnancy folic acid[45,110,111] and tight pre- and antenatal glycaemic control[112-118]. However, these interventions are difficult to achieve in the routine clinical environment for a number of reasons, including patient factors such as socioeconomic and education status, along with competing healthcare resource utilization.

The Atlantic DIP initiative involves healthcare professionals in antenatal centers along the Irish Atlantic Seaboard working to achieve the best outcome for pregnant women with diabetes. Since its establishment in 2005, we have introduced a number of structured, evidence-based interventions to work toward optimization of pregnancy outcomes. The changes developed and implemented over the last decade include: a regional prepregnancy care programme; regional combined diabetes/antenatal clinics with dedicated nurse specialists, obstetricians, and diabetologists; electronic recording of pregnancy outcomes; development of local guidelines for healthcare professionals[119]; development of patient information booklets[120]; a diabetes-in-pregnancy application for smart phones; and a web site[121]. In addition, we adapted a proactive approach to professional updates.

2.2. Study Objective

The Atlantic DIP researchers complete regular audits of clinical outcomes[58,71]. In this study pregnancy outcomes from 2005 - 2009 are compared with those from 2010 – 2014 in order to assess the impact of changes made to clinical service delivery during this time. We hypothesise that there has been a positive impact and expect to observe an improvement in pregnancy outcomes in the latter time period.

2.3 Methods

2.3.1 Study Design

This is a retrospective study of women with type 1 and type 2 diabetes with singleton pregnancies and registered in the Atlantic DIP programme between 2005 and 2014. Pregnancy outcomes were compared from 2005–2009 and 2010–2014.

2.3.2 Atlantic DIP Initiative

The Atlantic DIP Initiative was established in 2005 and aims to provide evidence-based care for women with diabetes mellitus before, during, and after pregnancy. It has a dual role of providing clinical care as well as undertaking observational cohort studies and randomized controlled trials aiming to enhance knowledge and improve management for women with diabetes in pregnancy. It comprises antenatal centers along the Irish Atlantic seaboard that provide diabetes antenatal care covering an urban/rural population of 500 000 with 11 000 deliveries annually. One hospital is a tertiary referral university center and the others are secondary care centers.

2.3.3 Changes made to Clinical Care Provision

A number of clinical practice interventions were made during this time period as follows.

A structured regional prepregnancy care programme was developed and implemented. Women of childbearing age attending routine diabetes clinics in the region are provided with written and verbal information and encouraged to attend the specialised clinics. General practitioners and women with diabetes in the region are also informed about the service through an annual mail shot. The prepregnancy care programme involves discussion of the timing of pregnancy, use of contraception while pregnancy preparation is ongoing, screening for and management of complications, blood pressure control, review of medications, optimization of glycaemic control, and initiation and/or intensification of insulin with a target HbA1c <43mmol/mol (6.1%) before a positive pregnancy test, prenatal folic acid use (5 mg for 12 weeks), education, prevention and treatment of hypoglycaemia, and discontinuation of teratogenic drugs.

Clinical care during pregnancy now involves combined antenatal clinics delivered by obstetricians and diabetologists with support from diabetes specialist nurses, midwives, and dietitians. Routine appointments are every 2 weeks, with the frequency increased/decreased as deemed necessary. Women are contacted by telephone on a weekly basis to facilitate regular dose adjustment of insulin.

All care is provided in a public capacity through the HSE and does not require any form of health insurance or payment.

Additional changes to clinical care provision over this decade include: electronic recording of outcomes via the Diamond Diabetes Information System (Hicom Woking, United Kingdom), development of local guidelines fashioned from national[44] and international guidelines[42,45], creation of a detailed patient information booklet[119], and a patient support app and web site[121]. Finally, a user-friendly, clinical practice booklet for professionals has been published and updated on three occasions[120].

2.3.4 Outcomes and Definitions

All women with diabetes for >6 months before the index pregnancy were included. Multiple pregnancies were excluded. Repeat pregnancies were included. Maternal HbA1c was measured during each trimester of pregnancy. Maternal BMI (weight in kilograms divided by the square of height in meters) was assessed at the 1st and each subsequent obstetrical visit. Target HbA1c was <48 mmol/mol (6.1%). Gestational hypertension was defined as a blood pressure >140/90 mm Hg, without proteinuria, on two or more occasions >6 hours apart, in a woman with normal blood pressure at her 1st obstetric visit. Preeclampsia was defined as onset of blood pressure >140/90 mm Hg and proteinuria >300 mg/24 h on two or more occasions >6 hours apart after 20 weeks gestation.

Miscarriage was defined as pregnancy loss before 24 weeks gestation. Stillbirth was defined as loss of a viable foetus after 24 weeks gestation. Stillbirth rate was calculated as the number of stillbirths per 1000 live- and stillbirths. Preterm delivery was defined as before 37 completed weeks of gestation, very preterm as <32 weeks, and extreme preterm as <28 weeks gestation. Large for gestational age (LGA) was defined as birth weight ≥ the

90th centile (for age and sex only), and small for gestational age (SGA) (for age and sex) as birth weight ≤ the 10th centile[122]. LGA and SGA were calculated manually by the Atlantic DIP data coordinator. All congenital malformations, major and minor, were included and coded according to European Surveillance of Congenital Anomalies (EUROCAT) Criteria[123]. Neonatal hypoglycaemia was diagnosed in the setting of a capillary glucose <2.0mmol/L on 2 consecutive readings

2.3.5 Statistical Analysis

Statistical analysis was carried out using Statistical Package for the Social Sciences (SPSS) version 21.0 (IBM). Hypothesis testing was performed on data of equal variance and normal distribution using an unpaired Student's *t* test. A χ^2 analysis was used to compare sample proportions. Data are expressed as n(%) or means ± standard deviation. Significance level was set at a p value of <0.05. Poisson distribution was used to obtain 95% confidence intervals for stillbirth rates.

2.4 Results

2.4.1 Participant Demographics (Table 2.1)

The study included 445 pregnancies that occurred in 304 women, 273 (61.0%) involving women with type 1 diabetes and 172 (39.0%) involving women with type 2 diabetes. They were divided into two groups for analysis: those delivered between 2005 and 2009 (n = 217, type 1 diabetes = 134, type 2 diabetes = 83) and those delivered between 2010 and 2014 (n = 228, type 1 diabetes = 139, type 2 diabetes = 89).

Table 2.1 Participant Demographics

	Period 1 2005-09 (n=217)	**Period 2 2010-14 (n=228)**	**p value**
Type 1 diabetes	134 (62)	139 (61)	
Type 2 diabetes	83 (38)	89 (39)	0.86
Age	31.7 ± 5.7	33.0 ± 5.1	0.01
White European	188 (87)	204 (89)	0.36
Parity	1.1 ± 1.3	1.0 ± 1.2	0.40

Data are expressed as n(%) or mean ± standard deviation.

Table 2.2 Pregnancy Preparation and Glycaemic Control

		Period 1 2005 – 2009 (n=217)	Period 2 2010 – 2014 (n=228)	P value
Folic Acid use prepregnancy		98 (45.2)	161 (71.0)	<0.001
Prepregnancy care attendance		51 (23.0)	112 (49.0)	<0.001
Teratogenic medication use at conception		10 (4.6)	6 (2.6)	0.39
Active smoker		29 (13.0)	24 (10.5)	0.38
1st trimester HbA1c <48mmol/mol (6.5%)		35 (16.0)	75 (33.0)	<0.001
1st trimester HbA1c <53mmol/mol (7.0%)		44 (20.0)	110 (48.0)	<0.001
1st trimester HbA1c mmol/mol (%)		62 ± 19 (7.8 ± 1.7)	53 ± 16 (7.0 ± 1.5)	<0.001
	Type 1 diabetes	64 ± 19 (8.0 ± 1.7)	56 ± 14 (7.3 ± 1.3)	0.003
	Type 2 diabetes	55 ± 17 (7.2 ± 1.6)	50 ± 19 (6.7 ± 1.7)	0.06
2nd trimester HbA1c mmol/mol (%)		49 ± 13 (6.6 ± 1.2)	45 ± 9 (6.3 ± 0.8)	<0.001
	Type 1 diabetes	52 ± 13 (6.9 ± 1.2)	46 ± 10 (6.4 ± 0.9)	0.001
	Type 2 diabetes	42 ± 10 (6.0 ± 0.9)	42 ± 7 (6.0 ± 0.6)	0.18
3rd trimester HbA1c mmol/mol (%)		45 ± 11 (6.3 ± 1.0)	44 ± 9 (6.2 ± 0.8)	0.32
	Type 1 diabetes	49 ± 12 (6.6 ± 1.1)	46 ± 9 (6.4 ± 0.8)	0.07
	Type 2 diabetes	42 ± 9 (6.0 ± 0.8)	42 ± 7 (6.0 ± 0.6)	0.60

Data are expressed as n(%) or mean ± standard deviation.

2.4.2 Pregnancy Preparation (Table 2.2)

The number of women attending structured prepregnancy care and taking folic acid before conception increased significantly across the time periods. Use of prepregnancy folic acid increased from 45 to 71% ($p<0.001$), and attendance for prepregnancy care more than doubled from 23 to 49% ($p<0.001$). There was a non-significant reduction in the number of women taking medications with teratogenic potential at conception (4.6 versus 2.6%; $p=0.3$). The number of women actively smoking has remained stable (13 versus 11%, $p=0.38$).

2.4.3 Glycaemic Control (Table 2.2)

The number of women entering the 1st trimester with a HbA1c of <48 mmol/mol (6.5%) increased from 16 to 33% ($p<0.001$) across the 2 time periods. The mean 1st trimester HbA1c reduced from 64 mmol/mol (8.0%) to 56 mmol/mol (7.3%) ($p=0.003$) in type 1 diabetes and 55 mmol/mol (7.2%) to 50 mmol/mol (6.7%) ($p=0.06$) in type 2 diabetes. Women who had a 1st trimester HbA1c <48 mmol/mol (6.5%) in our cohort were less likely to have miscarriages (2.6 versus 17%; $p<0.001$), and there was a trend toward less congenital malformations (3.6 versus 7.4%; $p=0.16$). The improvement in glycaemic control continues throughout the rest of pregnancy for women with type 1 diabetes. Those with type 2 diabetes maintained a mean HbA1c of 44 mmol/mol (6.0%) throughout trimesters 2 and 3 during both time periods.

2.4.4 Gestational Weight Gain / Body Mass Index (Table 2.3)

The percentage of women entering pregnancy with a BMI in the obese range (>30 kg/m^2) has increased from 29.0 to 43.0% ($p=0.002$). There has been an increase in the number of women demonstrating excessive GWG from 24 to 38% ($p=0.002$). This increase is seen in women who are overweight at the start of pregnancy, not in those who are normal weight or obese.

2.4.5 Maternal Outcomes (Table 2.3)

There was an overall rate of 55% for delivery by caesarean section with a trend toward more caesarean sections in the 2nd period (52 versus 57%;

p=0.30). There was an overall increase in elective caesarean deliveries, and this increase was seen more in women with type 1 diabetes (24 versus 33%; p=0.09) than type 2 diabetes (31 versus 35%; p=0.62). This is also higher than the population averages of 25.8% in the 1st time period and 28.1% in the 2nd. The overall rate of emergency caesarean section was static (25%), but there was a non-significant increase in those with type 1 diabetes (24 versus 29%; p=0.36) and a significant decrease for those with type 2 diabetes (28 versus 15%; p=0.04). Obese women were more likely to undergo elective caesarean sections than non-obese women (40 versus 27%; p=0.05) but were not more likely to undergo emergency caesarean sections (26 versus 24%). There was no change in rates of gestational hypertension or preeclampsia over time.

2.4.6 Neonatal Outcomes (Table 2.4)

Comparing the two time periods, there are no differences in birth outcomes. The following is a brief clinical description of the stillbirths that occurred during this study.

Period 1:

1. 35 weeks gestation, spontaneous labour with maternal diabetic ketoacidosis and foetal death.
2. 38 weeks gestation, foetal distress in labour with foetal death.
3. 28 weeks gestation, foetal death (foetal hydrops diagnosed during pregnancy).
4. 40 weeks gestation, foetal distress in labour with foetal death.
5. 38 weeks gestation, foetal distress in labour with foetal death.

Period 2:

1. 25 weeks gestation, foetal death in setting of maternal Guillain-Barre syndrome.

Incidence of congenital malformations and mean birth weight are also unchanged, as are rates of LGA and shoulder dystocia. There has been no increase in the numbers of SGA infants. There was been no change in

preterm delivery or in the number of babies experiencing neonatal hypoglycaemia or requiring neonatal intensive care unit (NICU) admission. The most common reasons for NICU admission were neonatal hypoglycaemia (28%), prematurity (23%), respiratory distress (5%), jaundice (2.5%), infection (2.5%), and congenital malformations (2.5%). One-third of babies were admitted for no medical reason, 21% for routine observation, and 12% for social reasons. There was no difference in rates of preterm deliveries.

Table 2.3 Maternal Body Mass Index and Pregnancy Outcomes

	Period 1 2005-09 (n=217)	**Period 2 2010-14 (n=228)**	**p value**
Caesarean delivery	113 (52.0)	130(57.0)	0.30
Type 1 diabetes	65 (49.0)	86 (62.0)	0.03
Type 2 diabetes	48 (58.0)	44 (49.4)	0.27
Caesarean delivery rate	60.0%	65.6%	
Background population caesarean delivery rate	25.8%	28.1%	
Elective caesarean	58 (27.0)	77 (33.7)	0.11
Type 1 diabetes	32 (24.0)	46 (33.0)	0.09
Type 2 diabetes	26 (31.0)	31 (34.8)	0.62
Emergency caesarean	55 (25.3)	53 (25.9)	0.61
Type 1 diabetes	32 (24.0)	40 (28.7)	0.36
Type 2 diabetes	23 (28.0)	13 (14.6)	0.04
Gestational hypertension	40 (18.4)	50 (22.0)	0.36
Pre-eclampsia	24 (11)	25 (11.0)	0.97
Booking BMI (kg/m^2)	29 ± 6.5	29.6 ± 6.3	0.34
Booking BMI >30kg/m^2	62 (29.0)	98 (43.0)	0.002
Excessive GWG	52 (24.0)	87 (38.0)	0.002
Excessive GWG in normal BMI*	19 (37.0)	24 (28.0)	
Excessive GWG in overweight BMI *	15 (29.0)	33 (38.0)	
Excessive GWG in obese BMI*	18 (35.0)	30 (35.0)	0.45

Data are expressed as n(%) or mean ± standard deviation. BMI: body mass index. GWG: gestational weight gain.
*Normal BMI= 18.5–24.9kg/m^2, overweight = 25.0 – 29.9kg/m^2 , obese = ≥30kg/m^2

Table 2.4 Neonatal Outcomes

	Period 1 2005-09 (n=217)	Period 2 2010-14 (n=228)	Period 1 versus period 2 p value
Live birth	182 (84.0)	197 (86.4)	0.45
Miscarriage	30 (14.0)	30 (13.2)	0.83
Stillbirth	5 (2.3)	1 (0.4)	0.12
Neonatal deaths	0	0	
Stillbirth Rate[1]	26.0	5.0	
(95% CI)	(8.5 – 60.8)	(0.1 – 28.0)	
Background population stillbirth rate[1]	4.9	4.2	
Delivery[2]	n=187	n=198	
Delivery < 37 weeks	60 (32.1)	67 (33.8)	0.71
Delivery < 34 weeks	44(23.5)	42 (21.2)	0.59
Delivery < 28 weeks	4 (2.1)	4 (2.0)	0.93
Congenital malformation	11 (5.9)	4 (2.0)	0.05
Neonatal hypoglycaemia	33 (17.6)	27 (13.6)	0.28
Shoulder dystocia	5 (2.7)	3 (1.5)	0.43
Macrosomia:			
>4.0kg	44(23.5)	53(26.8)	0.46
>4.5kg	12 (6.4)	15 (7.6)	0.64
Large for gestational age	46 (24.6)	57(28.8)	0.35
Small for gestational age	14 (7.5)	14 (7.1)	0.87
Mean birth weight (kg)	3.5 ± 0.8	3.5 ± 0.9	1.00
Neonatal intensive care unit admission[3]	n=182	n=197	
	105 (57.7)	100 (50.8)	0.18

Data are expressed as n(%) or mean ± standard deviation.
[1] per 1000 live births and stillbirths.
[2] excluding miscarriages
[3] all livebirths

2.5 Discussion

2.5.1 Summary and Discussion of Findings

Over the last decade, the Atlantic DIP initiative has introduced a number of changes to clinical practice in an attempt to optimize pregnancy outcomes for women with diabetes. This study presents pregnancy outcomes for women with type 1 and type 2 diabetes over this 10-year period. In order to assess for improvements over time, pregnancies are divided into two groups, those occurring from 2005 - 2009 and from 2010 - 2014. We observe improved pregnancy preparation, with increased attendance at prepregnancy care and use of folic acid prepregnancy. Glycaemic control is significantly better in the 1st and 2nd trimesters of pregnancy.

Despite the aforementioned improvements, this study highlights ongoing challenges. Hyperglycaemia is the primary driver of poor pregnancy outcome, and studies consistently show that tight glycaemic control before[115,124] and during[85] pregnancy, as well as during labor[125] decreases the risk of a poor outcome. In the United Kingdom, NICE 2015 guidelines advise a target HbA1c of <48 mmol/mol (6.5%)[42] during pregnancy. The 2017 ADA guidelines advise 42 - 48 mmol/mol (6.0 – 6.5%), and <42 mmol/mol (6.0%) if this is achievable without causing problematic hypoglycaemia[43]. Despite significant input, just 33% of our women are now achieving the target of 48 mmol/mol (6.5%), with 48% achieving a target of 53 mmol/mol (7.0%) in the 1st trimester (2010 – 2014). Furthermore, despite an overall improvement in glycaemic control across the two time periods, we have not observed a reduction in mean birth weight or frequency of LGA/macrosomia. This finding is consistent with prior work that revealed a high prevalence of LGA in offspring of women with type 1 diabetes, despite glucose levels obtained during self monitoring and HbA1c measurements indicating good control[66]. It is hoped that the introduction of technologies such as continuous glucose monitoring and closed loop systems into routine clinical practice will allow for better identification of glucose variability contributing to excessive foetal growth and more precise insulin dosing leading to improvements in glycaemic control and pregnancy outcomes[64,126].

In women with type 2 diabetes, the argument in favor of metformin use is gathering momentum, as taking large doses of insulin to overcome marked insulin resistance is associated with weight gain and is challenging to titrate without hypoglycaemia[127]. Metformin has been used in South Africa in pregnancies affected by type 2 diabetes since the 1970s, and perinatal mortality, although higher than the general obstetric population, was lower than in untreated women and similar to those who were treated with insulin[128]. In addition, there have been a number of systematic reviews and meta-analyses that favor metformin use in pregnancy[129,130]. However, there are no large randomized-controlled trials evaluating the efficacy of metformin in reducing adverse maternal and foetal outcomes in this population and we await the outcome of the Metformin in women with Type 2 diabetes in pregnancy (MiTy) trial to answer this question[127]. The results of the MiTy trial may lead to a change in clinical practice and provide an additional therapeutic option for women with type 2 diabetes.

We also observed an increase in rates of obesity and excessive GWG across the two study periods. The later issue will be explored in detail in chapter three of this thesis, however it is clear that significant improvements are also necessary in this area as both factors are associated with an increase in adverse pregnancy outcomes including macrosomia and LGA[131,132].

Finally, the proportion of women receiving a caesarean delivery has increased significantly to 62%, despite a reduction in malformations and improved glycaemic control. This is in excess of published rates internationally[133]. Although the timing of delivery is extremely important in women with diabetes, it is also important to avoid unnecessary operative deliveries. Caesarean delivery is not without risk, and complications such as wound infection can be seen more frequently in women with diabetes[134]. The underlying reasons for this increase in caesarean deliveries requires further evaluation but is likely that factors such as patient choice and the risk of litigation have a significant influence.

2.5.2 Strengths

This multi-center study contained detailed patient-level data that are presented to give a clear picture of pregnancy outcomes in women with pregestational diabetes. These data were recorded electronically at each patient encounter over the ten-year period and are highly accurate.

2.5.3 Limitations

The study is underpowered to adequately assess for differences in rates of rare events such as congenital anomaly and stillbirth, and so our findings must be interpreted with caution. Our small sample size is clearly demonstrated by the wide confidence intervals reported alongside the stillbirth rates. The frequency of LGA is lower than expected when compared to the frequency of macrosomia in the study and data from the UK NPID audit[63]. LGA and SGA were calculated manually in all the studies in this thesis and customised centile charts were not used. In order to assess the accuracy of our methodology, future analyses should consider the use of customised centiles and electronic calculation. We use a cutoff of <2.0mmol/L to define neonatal hypoglycaemia. However, this is not a universally accepted cutoff with the majority of UK units now using a threshold of 2.6mmol/L[93]. It is not possible to assess the impact of each individual intervention. In particular, we do not have accurate information on the level of interaction with our online resources. However, it may be argued that the combined effect of all the practice changes is what is clinically important. In addition, there are no national data available on obesity in pregnancy or GWG in Ireland, thus limiting comparison with our cohort with diabetes. Finally, we do not have information on the socioeconomic status of our participants.

2.5.4 Conclusions

Despite the positive findings associated with an improvement in clinical care delivery, women with type 1 and type 2 diabetes continue to have an increased risk of adverse pregnancy outcomes. Going forward it is hoped that emerging technologies will facilitate improved glycaemic control and successful strategies to manage maternal obesity and GWG will be developed and implemented.

Chapter 3: Gestational Weight Gain in Women with Diabetes

ATLANTIC-DIP: excessive gestational weight gain and pregnancy outcomes in women with gestational or pregestational diabetes mellitus. Egan AM, Dennedy MC, Al-Ramli W, Heerey A, Avalos G, Dunne F. J Clin Endocrinol Metab. 2014 Jan;99(1):212-9.
(Open Access Article)

3.1 Introduction

Women who have diabetes mellitus during pregnancy are at higher risk of adverse maternal and neonatal outcomes when compared to the background population without diabetes[22,57,58,63]. Among pregnant women in the Atlantic DIP cohort with a pregestational diagnosis of type 1 or type 2 diabetes mellitus, hereafter termed pregestational diabetes, we described an associated fivefold elevation in the stillbirth rate, a rate of perinatal mortality three and a half times higher and a doubling of the incidence of congenital malformation when compared to the background Irish population of pregnant women[50,58]. Moreover, there was a higher prevalence of LGA by a factor of 2 in offspring of women with pregestational diabetes[58]. The afforementioned results reflect outcomes of pregnancies between 2006 and 2007. While changes to clinical care provision have resulted in improvements in certain outcomes (chapter 2), these women continue to have significantly poorer outcomes when compared to their counterparts without diabetes[135]. Although the focus of this thesis is pregestational diabetes, the majority of diabetes complicating pregnancy is GDM. The Atlantic DIP initiative identified a prevalence of GDM which was 12.4% within a cohort of Irish women in which universal screening was applied using the IADPSG criteria[22,41]. Within this cohort, pregnancies complicated by GDM were associated with higher rates of gestational hypertension, polyhydramnios and delivery by caesarean section. Higher adverse neonatal events such as prematurity, LGA birthweight, neonatal unit admission, hypoglycaemia and respiratory distress were also associated with GDM[22,50].

Recent data have shown that excessive GWG represents a potential risk factor for adverse pregnancy outcomes[136-138]. In 2009, the IOM in the United States published guidelines describing BMI appropriate thresholds for GWG, upon which excessive weight gain during pregnancy could be defined (table 1.1)[87]. Thresholds were chosen based on historic data which described a linear increase in adverse neonatal and maternal outcomes in

assosication with GWG in women without GDM and pregestational diabetes. It is estimated that approximately 36% of mothers demonstrate excessive GWG and amongst women without diabetes this is robustly associated with LGA birthweight, caesarean delivery, and lower APGAR scores[136-138]. Additionally, in a cohort of largely Latina women with pregestational type 2 diabetes, excessive GWG according to IOM criteria was associated with significant perinatal morbidity, including LGA and macrosomia[139]. Finally, a retrospective study comprising mainly Hispanic women with and without GDM who were untreated with diet, exercise or antidiabetic medications during pregnancy, showed a higher incidence of LGA infants amongst those who gained excessive weight during their pregnancies[140].

3.2 Study Objective

On the basis of the afforementioned data, we hypothesised that in addition to the high risk conferred by a diagnosis of diabetes in pregnancy, excessive GWG confers further adverse risk. In this study, we describe for the first time, the effects of excessive GWG, defined using IOM criteria, within a cohort of predominantly White European women, all of whom were diagnosed with diabetes. We included women with pregestational diabetes along with women with IADPSG-diagnosed GDM to ensure a large cohort and to allow for comparison between both groups.

3.3 Methods

3.3.1 Study Design

In this study data collected by the Atlantic DIP initiative are retrospectively evaluated. One aspect of this previously described initiative (chapter 1, 1.7) comprises a number of prospective, observational studies on women with diabetes in pregnancy focusing on screening, management and follow up. The study area covers a regional population of 500,000 mixed urban and

rural dwellers across five antenatal centres with 11,000 deliveries per year. Research ethics committee approval was obtained from participating centres and data on women with diabetes in pregnancy were collected from study entry until 12 weeks post-partum. Women were recruited between September 2006 and April 2012. A cohort of women was extracted from Atlantic DIP with a diagnosis of either pregestational diabetes or GDM, with singleton pregnancies carried to term (>37 weeks gestation) and in whom weight and BMI had been recorded at the time of booking and the time of admission to the labor and delivery unit. Women were classified as having pregestational diabetes on the following basis: (i) an established diagnosis of type 1 or type 2 diabetes mellitus prior to conception; (ii) an HbA1c >48 mmol/mol (6.5%) in the 1st trimester; (iii) a new diagnosis of GDM according to IADPSG criteria[41] within the first 14 weeks of pregnancy. GDM was diagnosed using IADPSG criteria, following a 75g OGTT at 24-28 weeks gestation[41]. Each woman received standard advice on diet and exercise along with a dietician review. Education was provided to demonstrate self-directed glucose monitoring and to inform each woman regarding appropriate glycaemic targets. Women were reviewed on a fortnightly basis. At each visit weight was measured and an assessment of glycaemia was made. Insulin was commenced when blood glucose readings were outside of the following ranges on more than three successive days: fasting glucose 5.0mmol/L or a 2h post-prandial reading of 7.0mmol/L, according to local practice. Oral hypoglycaemic agents were not used in this study.

3.3.2 Outcomes and Definitions

BMI was calculated at 1st antenatal visit between 14 and 22 weeks and categorized according to WHO standards: underweight, <18.5 kg/m^2; normal, 18.5–24.9 kg/m^2; overweight, 25–29.9 kg/m^2; obese, ≥30 kg/m^2. The difference between the 1st recorded weight in the 2nd trimester and the pre-delivery weight was measured. Mean weight gain per week was then calculated and compared with IOM guidelines to assess if the upper limit of IOM recommended weight gain as per BMI category was breached (table 1.1)[87]. Subsequently, women were categorized into one of two groups

according to whether or not they demonstrated excessive or non-excessive GWG. Measured maternal outcomes included gestational hypertension (blood pressure >140/90 mm Hg on at least two occasions more than 6 h apart in women with normal booking blood pressure), preeclampsia [hypertension, proteinuria (>300 mg/24 h) onset >20 weeks] and caesarean delivery. Foetal / neonatal outcomes examined included LGA (>90th centile by gestational age), macrosomia (birth weight >4kg) and SGA (<10th centile by gestational age)[122]. Gestational age was determined at booking visit using obstetric ultrasound. Data were prospectively recorded using an optimized digital database, namely DIAMOND (Hicom, Woking, UK).

3.3.3 Statistical Analysis

Data were analysed using SPSS Version 20.0 (IBM, Chicago, IL). Multivariate analyses were performed and odds ratios calculated using a stepwise, backward logistic regression analysis adjusted for the following covariates; age, parity, ethnicity, use of insulin, booking BMI category and cigarette smoking. Hypothesis testing was performed on data of equal variance and normal distribution using an unpaired Student's t-test. Chi squared analysis was used to compare sample proportions. Data were expressed as n(%), means ± standard deviation of the mean, adjusted odds ratios (aOR) and 95% confidence intervals (CI). Statistical significance was accepted when the 95% CI did not contain one (regression analyses / ratios) or zero (multiple group comparisons / means). The significance level (α) was accepted when <0.05 for two-tailed analyses.

3.4 Results

3.4.1 Participant Demographics

Data from a total cohort of 802 women were analysed. This group comprised 543 (68%) women with GDM and 259 (32%) with pregestational diabetes, of whom 169 (65%) had type 1 and 90 (35%) had type 2 diabetes. Table 3.1 outlines the demographic details for these women. In total, 472 (59%) women demonstrated excessive GWG. Within this group, 108 (23%) had type 1 diabetes, 57 (12%) had type 2 diabetes and 307 (65%) had GDM.

Table 3.2 outlines the mean weight gain per week in the 2nd and 3rd trimester for each BMI category. The mean booking BMI was similar in those with excessive and non-excessive GWG but a higher percentage of women in the excessive weight gain group had a booking BMI within the overweight category (38% for excessive versus 25% for non-excessive). A higher percentage of women with pregestational diabetes demonstrated excessive GWG (64%) when compared to women with GDM (57%) but this difference is not statistically significant (p=0.05). There was no difference in age, ethnicity, smoking status, parity, gravidity or insulin use during pregnancy between those who did and did not have excessive GWG. We further analysed the effects of weight gain on pregnancy outcomes specific to the diagnoses of pregestational diabetes and GDM in these women.

3.4.2 Women with Pregestational Diabetes

Amongst the 259 women with a diagnosis of pregestational diabetes, excessive GWG occurred in 165 (64%) with similar proportions displaying excessive weight gain in women with Type 1 and Type 2 diabetes respectively. Women with pregestational diabetes had an overall lower BMI at 1st antenatal visit than their GDM counterparts (28.54 ± 5.8 kg/m^2 versus 31.28 ± 6.93 kg/m^2, p<0.001), but amongst those with pregestational diabtetes demonstrating excessive GWG, booking BMI was higher than those with non-excessive GWG (29.4 ± 5.7 kg/m^2 versus 27.0 ± 7.7 kg/m^2, p=0.01). Consequently there were higher proportions with a booking BMI in the overweight and obese categories within the excessive weight gain compared with the non-excessive weight gain group (44% versus 27% for overweight and 37% versus 25% for obese). The use of insulin during pregnancy was similar for both groups as were the average 1st and 3rd trimester HbA1c levels (table 3.3).

Excessive GWG was associated with higher odds for LGA birth weight [aOR 3.97 (1.85 to 8·53); p<0.001] and macrosomia [aOR 3.58 (1.77 to 7.24); p<0.001] (table 3.5). As the majority of women with pregestational diabetes were taking insulin during pregnancy, the additive effects of insulin therapy were not analysed for this group.

3.4.3 Women with GDM

Among women with GDM, 307 (57%) demonstrated excessive GWG. These women were younger than those who did not have excessive weight gain (32·9 ± 5·39 years versus 34·20 ± 4·73 years, p=0·01). A higher percentage of those in the excessive weight gain group were overweight (35% versus 24%) and a lower proportion obese (48% versus 56%) at time of 1st antenatal visit compared with those in the non-excessive weight gain group. Mean BMI at booking was similar for excessive and non-excessive GWG groups (30.75 ± 6.60 kg/m^2 versus 31.86 ± 7.30 kg/m^2, p=0.06). There were no significant differences in ethnicity, parity, gravidity, smoking status, glucose levels at time of OGTT, percentage of women treated with insulin or 3rd trimester HbA1c between the groups (table 3.4).

There were higher odds for LGA birthweight [aOR 2·01 (1.24 to 3.25); p=0.01] and macrosomia [aOR 2.17 (1.32 to 3.55); p<0.01] in women demonstrating excessive weight gain. These effects of excessive GWG were further compounded by an additive effect of insulin therapy. The combined effects of insulin and excessive GWG increased the odds for LGA infants [aOR 2.80 (1.23, 6.38); p=0.01] and macrosomia [aOR 5.63 (2.16 to 14.69); p<0.001] above the individual contribution of either variable. Interestingly, women with GDM who were taking insulin gained less weight than those not on insulin therapy (0.62 +/- 0.30 kg/week versus 0.84 +/- 0.58 kg/week; p<0.0001). Excessive GWG was also associated with higher odds for gestational hypertension [aOR 1.72(1.04 to 2.85); p=0.04] (table 3.6).

Table 3.1: Demographic Characteristics of Included Women (Pregestational Diabetes and GDM) (n=802)

	Excessive weight gain	Non-excessive weight gain	p value
n (%)	472 (59%)	330 (41%)	
Diabetes Type			
Type 1 diabetes	108 (23%)	61 (18%)	
Type 2 diabetes	57 (12%)	33 (10%)	
GDM	307 (65%)	236 (72%)	
Age (years)	32·98 ± 5.43	33·54 ± 4.94	0.14
Smoker	46 (10%)	26 (8%)	0.36
White European	403 (85%)	281 (85%)	0.93
Parity	1.08 ± 1.23	1.24 ± 1.52	0.10
Gravida	2.53 ± 1.68	2.71 ± 194	0.16
Booking BMI (kg/m^2)	30.27 ± 6.33	30.48 ± 7.2	0.66
Booking BMI Category			
Normal	85 (18%)	90(27%)	
Overweight	179(38%)	82 (25%)	
Obese	208 (44%)	155 (47%)	<0.001
Insulin use during pregnancy	264 (56%)	164 (50%)	0.08

Data are expressed as n(%) or mean ± standard deviation.
GDM: gestational diabetes mellitus; BMI: body mass index.

Table 3.2: Mean Weight Gain in Women during Trimesters Two and Three (kg/week)

Diabetes category	BMI category	Excessive weight gain group		Non-excessive weight gain group	
		n (%)	Mean weight gain (kg/week)	n (%)	Mean weight gain (kg/week)
All participants	Normal	85 (18%)	0.86 ± 0.31	90 (27%)	0.36 ± 0.10
	Overweight	179 (38%)	0.73 ± 0.29	82 (25%)	0.24 ± 0.08
	Obese	208 (44%)	0.66 ± 0.30	155 (47%)	0.13 ± 0.14
GDM	Normal	54 (18%)	0.98 ± 0.45	46 (20%)	0.35 ± 0.07
	Overweight	106 (35%)	0.84 ± 0.50	57 (24%)	0.23 ± 0.09
	Obese	147 (48%)	0.70 ± 0.33	132 (56%)	0.12 ± 0.15
Pregestational diabetes	Normal	31 (19%)	0.64 ± 0.12	44 (47%)	0.37 ± 0.10
	Overweight	73 (44%)	0.57 ± 0.18	25 (27%)	0.25 ± 0.07
	Obese	61 (37%)	0.57 ± 0.22	23 (25%)	0.20 ± 0.06

Data are expressed as n(%) or mean ± standard deviation.
GDM: gestational diabetes mellitus; BMI: body mass index.

Table 3.3 Women with Pregestational Diabetes (n=259): Demographic Characteristics and Prevalence of Adverse Outcomes

	Excessive Weight Gain	Non-Excessive Weight Gain	p value
n (%)	165 (64%)	94 (36%)	
Diabetes Type			
Type 1 Diabetes	108 (65%)	61 (65%)	
Type 2 Diabetes	57 (35%)	33 (35%)	
Age (years)	33.00 ± 5·52	31.89 ± 5.10	0.11
Smoker	18 (11%)	13 (14%)	0.49
White European	149 (90%)	81 (86%)	0.31
Parity	1.06 ± 1.22	1.04 ± 1.34	0.90
Gravida	2.59 ± 1.96	2.49 ± 1.68	0.68
Booking BMI (kg/m^2)	29.4 ± 5.7	27.03 ± 5.7	<0.01
Booking BMI Category			
Normal	31 (19%)	44(47%)	
Overweight	73 (44%)	25 (27%)	<0.001
Obese	61 (37%)	23 (25%)	
Insulin use during pregnancy	157 (95%)	85 (90%)	0·14
1st Trimester HbA1c (%)	51 ± 16 (6.8 ± 1.5)	53 ± 14.2 (7.0 ± 1.3)	0.46
3rd Trimester HbA1c (%)	50 ± 14 (6.7 ± 1.3)	49 ± 15 (6.6 ± 1.4)	0.95
Normal Vaginal Delivery	58 (35.2%)	47 (50%)	0.02
Adverse outcomes			
Pre-eclampsia	22 (13.3%)	11 (11.7%)	0.70
Gestational Hypertension	43 (26.1%)	20 (21.3%)	0.40
Caesarean Delivery	107 (64.8%)	47 (50%)	0.02
Macrosomia	55 (33.3%)	13 (13.8%)	<0.001
LGA	53 (32.1%)	12 (12.8%)	<0.001
SGA	9 (5.5%)	9(9.6%)	<0.01

Data are expressed as n(%) or mean ± standard deviation.
BMI: body mass index; LGA: large for gestational age; SGA: small for gestational age.

Table 3.4: Women with GDM (n=543): Demographics and Prevalence of Adverse Outcomes

	Excessive Weight Gain	Non-Excessive Weight Gain	p value
n (%)	307 (57%)	236 (43%)	
Age (years)	32·97 ± 5·39	34·20 ± 4·73	0.01
Smoker	28 (9%)	13 (6%)	0.11
White European	254 (83%)	200 (85%)	0.53
Parity	1.09 ± 1.23	1.32 ± 1.58	0.06
Gravida	2.50 ± 1.51	2.80 ± 2.03	0.05
Booking BMI (kg/m^2)	30.75 ± 6.60	31.86 ± 7.30	0.06
Booking BMI Category			
Normal	54 (18%)	46 (20%)	
Overweight	106 (35%)	57 (24%)	
Obese	147 (48%)	132 (56%)	0.03
Glucose 0 mins (mmol/L)	5.28 ± 0.90	5.16 ± 0.91	0.13
Glucose 60 mins (mmol/L)	10.18 ± 2·17	10.32 ± 1·59	0.41
Glucose 120mins (mmol/L)	7.85 ± 2.20	8.20 ± 2.14	0.06
Insulin use during pregnancy	107 (34.9%)	79 (33.5%)	0.74
3^{rd} Trimester HbA1c (%)	37 ± 4 (5.5 ± 0.4)	37 ± 5.5 (5.5 ± 0.5)	0.73
Normal Vaginal Delivery	186 (60.6%)	134 (56.8%)	0.37
Adverse outcomes			
Pre-eclampsia	27 (8.5%)	14 (5.9%)	0.21
Gestational Hypertension	56 (18.2%)	29 (12.3%)	0.06
Caesarean Delivery	121 (39.4%)	102 (43.2%)	0.37
Macrosomia	67 (21.8%)	35 (14.8%)	0.04
LGA	71 (23.1%)	30 (12.7%)	<0.01
SGA	18 (5.9%)	15 (6.4%)	0.05

Data are expressed as n(%) or mean ± standard deviation.
BMI: body mass index; GDM: gestational diabetes mellitus; LGA: large for gestational age; SGA: small for gestational age.

Table 3.5: Multivariable Analysis of Adverse Outcomes Associated with Excessive GWG in Women with Pregestational Diabetes

Outcome	Excessive GWG	
	aOR (95% CI)	p value
Pre-eclampsia	0.48 (0.15 - 1.54)	0.22
Gestational Hypertension	0.79 (0.32 - 1.96)	0.62
Caesarean Delivery	1.61 (0.74 – 3.51)	0.23
Macrosomia	3.58 (1.77 - 7.24)	<0.001
LGA	3.97 (1.85 - 8.53)	<0.001
SGA	0.77 (0.26 – 2.28)	0.63

Adjusted for age, parity, ethnicity, use of insulin, booking BMI category and cigarette smoking.
aOR: Adjusted odds ratio.
LGA: large for gestational age; SGA: small for gestational age.

Table 3.6: Multivariable Analysis of Adverse Outcomes Associated with Excessive GWG in Women with GDM

Outcome	Excessive GWG		Excessive GWG and Insulin use	
	aOR (95% CI)	p value	aOR (95% CI)	p value
Pre-eclampsia	1.59 (0.81 - 3.12)	0.18	1.62 (0.79 - 3.32)	0.19
Gestational Hypertension	1.72 (1.04 - 2.85)	0.04	1.79 (1.05 - 3.07)	0.01
Caesarean Delivery	0.84 (0.51 – 1.37)	0.48	1.32 (0.63 – 2.73)	0.44
Macrosomia	2.17 (1.32 - 3.55)	<0.01	5.63 (2.16 - 14.69)	<0.001
LGA	2.01 (1.24 - 3.25)	0.01	2.80 (1.23 - 6.38)	0.01
SGA	1.01 (0.47 – 2.18)	0.98	0.85 (0.21 – 3.4)	0.81

Adjusted for age, parity, ethnicity, use of insulin, booking BMI category and cigarette smoking.
aOR: Adjusted odds ratio.
GDM: gestational diabetes mellitus; LGA: large for gestational age; SGA: small for gestational age.

3.5 Discussion

3.5.1 Summary and Discussion of Findings

Pregestational diabetes and GDM represent high-risk conditions individually associated with adverse maternal and neonatal outcomes[22,57,71]. We show that in the already high-risk settings of diabetes in pregnancy, excessive GWG is significantly associated with an additive risk for LGA birthweight, macrosomia and gestational hypertension. This is the first time that an analysis of GWG has been undertaken, using the IOM criteria in a large, cohort of women with diabetes.

Overall, more than half of women with pregestational diabetes and GDM gained excessive weight during pregnancy and this occurred in spite of an intensive, multi-disciplinary lifestyle intervention programme in the setting of combined diabetes/obstetric care. These characteristics are similar to those in a previous study of women with GDM that reported 41 – 57.9% excessive GWG depending on BMI category[140]. Given the large proportion of women affected by excessive weight gain, the challenge relating to its management is apparent.

The background BMI was higher in women with diabetes when compared to previous analyses of normoglycaemic women within the Atlantic-DIP cohort[131,141]. Two observations within the current study, relating to patterns of weight gain in the context of high BMI were interesting. Firstly, women who were overweight displayed higher GWG when compared to those who were of normal or obese BMI. Secondly, women who gained excessive weight tended to be younger than those who did not. While these results cannot be wholly explained by the current analysis, they may highlight a bias in the emphasis upon management of diabetes during pregnancy amongst care providers, whereby the message relating to weight management is reinforced more vigorously in obese rather than overweight women. These data also suggest that older women, who have significant concerns relating to age-related obstetric outcomes may be more likely to comply with lifestyle advice during pregnancy, in order to minimize

perceived additional risk.

Our principal finding relates to neonatal outcome, specifically highlighting the effects of excessive weight gain to confer a higher risk of LGA birth weight and macrosomia. These data conform to those of other authors who have shown similar effects of excessive weight gain on birth weight for non-diabetic or mixed populations of pregnant women[138-140,142,143]. However, our data are novel in presenting these findings for the first time in a high-risk sample, comprising exclusively women with a diagnosis of diabetes who were managed intensively throughout pregnancy according to international guidelines. The additive risk presented by excessive GWG is concerning when taken in the context of clinical complications associated with LGA birth weight and macrosomia including a two to three fold higher risk of intrauterine death, shoulder dystocia and consequent brachial plexus injuries, in addition to higher rates of caesarean section[144,145]. Longitudinal observational studies have also demonstrated poorer long-term outcomes for these infants including childhood obesity, asthma and in later life the metabolic syndrome, type 2 diabetes, and cancer[145,146]. There are data that support an improvement in obstetric outcomes using a management programme to prevent excessive GWG, however these studies include selected groups of women and may not be applicable to women with diabetes in pregnancy[147-149]. Additionally, other evidence suggests that although lifestyle intervention is associated with restricted GWG, there is not clear evidence for a reduction in adverse outcomes as a result, particularly in the overweight and obese population[150]. These findings combined with our data make a clear case for the design, implementation and evaluation of intensive "weight-centred" management programmes for all women with diabetes during pregnancy, irrespective of antenatal BMI. We propose that appropriate control of GWG, within the limits set by IOM guidelines will avoid potential neonatal complications relating to birth weight and will also improve glycaemic control, thereby reducing baseline risk related to diabetes.

Another interesting observation presented herein is the combined effects of

excessive GWG and insulin use in women with GDM, which further increased the odds for higher birth weight. Interestingly, women with GDM taking insulin gained less weight overall when compared to their counterparts who were managed using lifestyle measures only. The potential mechanisms underlying these effects merit further discussion. The transplacental passage of exogenous insulin is negligible and therefore, our observations are unlikely to result from a direct effect of exogenous insulin within the foetal circuit[151,152]. However, placentae of women with GDM who are treated with insulin demonstrate significantly higher trophoblastic expression of insulin receptors when compared to their non-insulin treated counterparts[153]. Moreover trophoblastic insulin receptor activation results in increased downstream signalling of mitogen-activated protein kinases responsible for trophoblastic expansion[154]. Abnormal and prolonged trophoblastic expansion consequent to insulin therapy, combined with so-called maternal over-nutrition may underpin the additive risks of insulin and excessive GWG on neonatal birth weight. Further scientific studies of mechanism are necessary to investigate this.

Clinically, our findings relating to insulin therapy in women GDM gaining excessive weight during pregnancy are somewhat surprising. The principal aim of instituting insulin therapy in GDM is to improve maternal and neonatal outcomes. While our data may represent the influence of poorer baseline glycaemic control in women with GDM who go on to require insulin, it also highlights the importance of added attention to weight management in pregnancy within this cohort, above that of glycaemic control alone. Traditionally, we have used exogenous insulin as first-line pharmacologic management of GDM. It is only recently that convincing data suggesting the safety and efficacy of metformin have emerged[155]. Our findings add to the debate that suggests metformin may represent a suitable first-line therapy for future management of GDM. Metformin crosses the placenta during pregnancy and hence use of this agent during pregnancy is not currently routine[156]. Nonetheless, encouraging data have supported the safety profile of metformin use with or without supplemental insulin in women with GDM, with some studies suggesting increased insulin

sensitivity and improved longer-term outcomes in offspring[155,157,158]. Other work has demonstrated that pregnant women treated with metformin although heavier in the 1st trimester, gained less weight in pregnancy and lost less weight in the 1st year post partum. However, their offspring weighed more at one year compared to children not exposed to metformin[159]. While a large randomised controlled trial found that metformin has no significant effect on birth weight percentile in obese pregnant women without diabetes[160], the ongoing EMERGE (Effectiveness of MEtformin in addition to usual care in the Reduction of GEstational diabetes mellitus) trial will provide further insights into the effectiveness of metformin in women with GDM[161]. The overall objective of the EMERGE trial is to determine whether metformin and usual care, compared to placebo and usual care (introduced at the time of initial diagnosis of GDM), reduces a) the need for insulin use, or hyperglycaemia (primary outcome measure); b) excessive maternal weight gain; c) maternal and neonatal morbidities and, d) cost of treatment for women with GDM.

The association of GWG with gestational hypertension in women with GDM highlighted the influence of weight gain and so-called maternal "over-nutrition" in the development of an adverse metabolic milieu. Excessive GWG did not produce an additive risk for the development of pre-eclampsia in this group of largely high BMI women with a high-baseline risk of pre-eclampsia by virtue of the diagnosis of diabetes[22,71].

3.5.2 Strengths

Overall this was a robust, nested cohort analysis performed retrospectively using data collected and managed prospectively within the Atlantic-DIP study design using a validated database. Acknowledging the limitations associated with observational study design and associated influence of measured and unmeasured covariates, we have used adjusted multivariate regression analysis to provide convincing and strong associations between adverse pregnancy outcomes and excessive GWG. We also used strong, validated classification systems for the definition of GWG and BMI.

3.5.3 Limitations

Potential covariates, which have not been measured during this study include those of glycaemic control in early pregnancy for women with GDM and socio-economic status. Both of these are difficult to measure and require dedicated prospective study design. Glycaemic control in GDM during early pregnancy may influence pregnancy outcome and future requirement for institution of insulin therapy. However, under current guidelines, the diagnosis of GDM is not made until 24 – 28 weeks and hence analysis was not possible during this study. We include 3rd trimester HbA1c as an index of glycaemic control post diagnosis of GDM and in women with pregestational diabetes we include both 1st and 3rd trimester HbA1c. A lack of significant difference between the excessive and non-excessive groups in relation to HbA1c supports our conclusion that excessive GWG is associated with adverse outcomes independent of glycaemic control during pregnancy. Socio-economic status was also difficult to adjust for in the context of the mixed urban-rural characteristics of the population of pregnant women included in this study.

We did not have accurate measurement of pre-gestational weights for calculation of BMI. We did not use self-reported maternal weight in our analysis due to the risk of recall bias. Booking BMI was therefore calculated between 14 and 22 weeks and used as a surrogate measurement for pre-gestational BMI. This methodology is supported by a study by Fattah et al, who demonstrate no change in mean maternal weight or body composition over the 1st trimester of pregnancy in a cohort of non-diabetic women[162]. We also back-calculated pre-gestational weight, assuming a 1st trimester weight gain in the midrange (subtraction of 1kg) of IOM guidelines and this did not result in a change of BMI category for any study participant[87,146]. While limited by the absence of weight measurements from early pregnancy, our data nonetheless provide clinically relevant data which clearly relate the effects of excessive GWG over the 2nd and 3rd trimesters to adverse pregnancy outcome in a cohort of women with diabetes during pregnancy. Larger prospective studies, which collect data in the 1st trimester of pregnancy are required to further address this aspect of study design and

also to investigate changes across BMI subcategories as well as subcategories of pregestational diabetes.

3.5.4 Conclusions

For the first time, we apply the 2009 IOM guidelines for GWG in a sample of women with pregestational and GDM from a community who have undergone universal screening for GDM. We provide robust data, of clinical significance that will guide multi-disciplinary health-care teams in managing this high-risk patient population. We advocate the use of IOM recommendations to classify GWG in women with diabetes and recommend targeted management of GWG in these women, particularly those who go on to commence insulin therapy. Future research focusing prospectively on active management to prevent or reverse GWG gain will highlight the potential benefit in terms of maternofoetal outcomes for these women and their offspring.

Chapter 4: Diabetic Retinopathy in Women with Type 1 and Type 2 Diabetes in Pregnancy

Diabetic retinopathy in pregnancy: a population-based study of women with pregestational diabetes.
Egan AM, McVicker L, Heerey A, Carmody L, Harney F, Dunne FP.
J Diabetes Res. 2015;2015:310239.
(Open Access Article)

4.1 Introduction

Deterioration of diabetic retinopathy during pregnancy is well described in women with pregestational diabetes mellitus[59,60]. This progression is influenced by multiple factors including the pregnancy itself, glycaemic control before and during pregnancy and the presence of pre-existing retinopathy[163,164]. Maternal medical complications including gestational hypertension, diabetic nephropathy and preeclampsia are also associated with progression of retinopathy[89,165]. Unfortunately, study sample size has frequently limited the evaluation of additional risk factors and many studies predate the era of modern diabetes care in pregnancy which includes tight glycaemic control and blood pressure management[59,60,166,167]. Additionally, there are no data on screening rates within populations or on factors associated with receiving adequate retinal examinations during pregnancy.

The Atlantic initiative was established in 2005 and represents five antenatal centres along the Irish Atlantic seaboard, covering a population of 500,000 mixed urban and rural dwellers. The group offers women specialist-led, evidence-based care before, during and after pregnancy and has significantly improved local outcomes in women with diabetes in pregnancy[71].

4.2 Study Objective

In this study we review the frequency of retinal examination during pregnancy in the Atlantic DIP cohort and examine maternal factors associated with receiving the optimal number of examinations.
Additionally, we document the progression of diabetic retinopathy during pregnancy and factors associated with this progression.

4.3 Methods

4.3.1 Study Design

This study was designed as an observational study of retinopathy status during pregnancy in women with pregestational diabetes. Research ethics committee approval was obtained and women were recruited between September 2006 and December 2012. Women with singleton pregnancies who provided informed consent were included. As per previous studies, women were classified as having pregestational diabetes on the following basis: 1) an established diagnosis of type 1 or type 2 diabetes prior to conception or 2) a HbA1c > 48mmol/mol (6.5%) in the 1st trimester. Data were collected from study entry until 12 weeks postpartum using an optimized digital database, namely DIAMOND (Hicom, Woking, UK)[86].

4.3.2 Procedures

Prior to pregnancy, during annual review appointments, all women were advised regarding the need to plan pregnancy and were offered the opportunity to attend a dedicated, prepregnancy service. During pregnancy, each woman received standard advice on diet and exercise along with a dietician review. Education was provided on self-directed glucose monitoring and each woman was advised on glycaemic targets. Women were reviewed on a fortnightly basis and telephoned on a weekly basis. Insulin was introduced (in the setting of type 2 diabetes) or adjusted if home glucose readings were outside the following ranges on more than three consecutive days: fasting glucose 5.0 mmol/L or a 2-hour postprandial reading of 7.0 mmol/L. Oral hypoglycaemic agents were not used during the study period. Retinal screening should occur at least twice during pregnancy in separate trimesters and if established retinopathy is present, then retinal examination should take place more frequently[119]. For the purposes of this study, we accepted at least two retinal evaluations in separate trimesters as adequate. During the study period, retinal examination took place in the locality of each antenatal centre and results were forwarded to the respective centre. At each visit, visual acuity was measured bilaterally using the Snellen chart. The pupils were then dilated with tropicamide 1% and ophthalmological examinations performed using a two-field photography system. An accredited retinal grader reviewed these images. If photo

screening was not performed or if the images were abnormal, an experienced ophthalmologist performed an eye examination. Progression was defined as at least one stage of deterioration of diabetic retinopathy and/or development of diabetic macular edema on at least one eye. Grading standards as outlined by the National Screening Committee in the United Kingdom were followed (table 4.1)[168]. Antihypertensive therapy was initiated when blood pressure was ≥ 135/85mmHg. Labetalol was the first choice antihypertensive agent, followed by methyldopa when needed.

4.3.3 Statistical Analysis

Data were analysed using SPSS version 20.0 (IBM). Hypothesis testing was performed on the data of equal variance and normal distribution using an unpaired Student's *t* test. The Mann-Whitney U test was used as the equivalent nonparametric test. Chi squared analysis was used to compare sample proportions. Binary logistic regression was utilized to assess the association of multiple covariates with receipt of adequate retinal evaluations and the progression of retinopathy. Data are expressed as n(%), means ± standard deviation of the mean, aOR, and 95% CI. Statistical significance was accepted when the 95% CI did not contain one (regression analyses/ratios) or zero (multiple group comparisons/means). The significance level (α) was accepted when <0.05 for two tailed analyses.

Table 4.1 Classification of Diabetic Retinopathy[168]

Grade	Description	Lesion
R0	No retinopathy	no apparent retinopathy
R1	Background retinopathy	Microaneurysm(s) Retinal haemorrhage(s) ± any exudate
R2	Pre-proliferative retinopathy	Venous beading, venous loop or reduplication Intraretinal microvascular abnormality (IRMA) Multiple deep, round or blot haemorrhages
R3	Proliferative retinopathy	New vessels on disc (NVD) New vessels elsewhere (NVE) Pre-retinal or vitreous haemorrhage Pre-retinal fibrosis ± tractional retinal detachment
M0	No maculopathy	No apparent maculopathy
M1	Maculopathy present	Exudate within 1 disc diameter (DD) of the centre of the fovea Circinate or group of exudates within the macula Retinal thickening within 1DD of the centre of the fovea (if stereo available) Any microaneurysms or haemorrhage within 1DD of the centre of the foveal only if associated with a best VA of ≤ 6/12 (if no stereo)

4.4 Results

4.4.1 Participant Demographics

We identified 307 women with pregestational diabetes who delivered after 28 gestational weeks from the Atlantic DIP database. This cohort comprised 208 (67.8%) women with type 1 diabetes and 99 (32.2%) women with type 2 diabetes. The majority of women were of White European ethnicity (n=278, 90.6%). There were 296 (96.4%) live births and 11 (3.6%) stillbirths.

4.4.2 Retinal Screening

Overall, 217 (70.7%) of 307 women had retinal evaluation at least once during pregnancy and 185 (60.3%) had an adequate number of examinations. Of the 32 women who had screening on one occasion only, 29 (90.6%) had no retinopathy and 3 (9.4%) had background retinopathy. Table 4.2 outlines the characteristics of those who received an adequate number of examinations versus those who did not. Those who received an adequate number of retinal evaluations were older (32.9 ± 5.3 versus 31.5 ± 5.4 years, p=0.02) and a higher proportion was of White European ethnicity (94.1% versus 85.2%, p=0.01). There was no difference in gravida; parity; 1st or 3rd trimester HbA1c; or smoking status between the two groups. Among women with type 1 diabetes, 64.4% received an adequate number of examinations, compared with 51.5% of women with type 2 diabetes. A higher proportion of women who received appropriate screening had attended prepregnancy care (58.4% versus 17.2%, p<0.001) and taken folic acid preconceptually (69.7% versus 54.1%, p=0.001). A higher proportion of women received adequate examinations in the years 2009 to 2012 compared with the years 2006 to 2008 (74.1% versus 25.9%).

4.4.3 Maternal Factors Associated with Retinal Screening

A logistic regression model was completed to further examine maternal factors associated with receiving an adequate frequency of ophthalmological evaluation in pregnancy. The results are outlined in table 4.3 and identified attendance at prepregnancy care as the only maternal factor significantly

associated with receiving appropriate screening [odds ratio 6.23; CI 3.39 – 11.46 (p<0.001)].

4.4.4 Retinopathy Progression

On evaluation of those patients who received two or more retinal evaluations (n=185), 48 (25.9%) had retinopathy progression during pregnancy. This represents 15.6% of all included patients (n=307). Table 4.4 further outlines the characteristics of the women including baseline retinal findings. A higher proportion of women with type 1 diabetes progressed compared to women with type 2 diabetes (31.3% versus 11.7%, p=0.001). Those women who demonstrated progression had on average, a longer duration of diabetes (14.43 ± 8.42 versus 9.79 ± 8.36 years, p<0.001). Although there was a higher frequency of preeclampsia in the group that experienced progression, this was not significant (14.6% versus 12.4%, p=0.80). However, those that did progress had a significantly higher systolic blood pressure at their initial antenatal visit (128.6 ± 18.0 versus 122.1 ± 13.0mmHg, p=0.03). Additionally, 1st trimester HbA1c was higher [61 versus 53 mmol/mol (7.7 versus 7.0%), p=0.01)] and the drop in HbA1c between 1st and 3rd trimester HbA1c greater (15 versus 8 mmol/mol (1.4 versus 0.7%), p=0.004)] among those women who had disease progression. There was no significant difference in rates of excessive GWG, smoking status or BMI between the two groups.

Of those women who developed progression (n=48), 32 (66.7%) had no retinopathy at baseline. A total of 26 (54.2%) women progressed from no retinopathy to level 1 (background) retinopathy only. A further 7 (14.6%) progressed from level 1 to level 2 (pre-proliferative) retinopathy and 6 women (12.5%) progressed to level 3 (proliferative) retinopathy and required laser therapy. Two women in the latter group had also received prepregnancy laser therapy. Finally, 6 (12.5%) women developed mild maculopathy and three (6.3%) experienced a worsening of preexisting maculopathy and required laser therapy. Among the group with maculopathy development (n= 9), 4 (44.4%) women received prepregnancy laser therapy.

4.4.5 Maternal Factors Associated with Retinopathy Progression

Logistic regression analysis revealed that increasing booking systolic blood pressure (OR 1.03, CI 1.01 – 1.06, p=0.02) and greater drop in HbA1c between 1st and 3rd trimesters of pregnancy (OR 2.05, CI 1.09 – 3.87, p=0.03) significantly increased the odds of retinopathy progression. Duration of diabetes, diabetes type and 1st trimester HbA1c were not associated with increased odds of progression and these results are outlined in table 4.6.

Table 4.2: Characteristics of Women who received an Adequate Number of Retinal Examinations versus those who did not (n=307)

	Adequate number of retinal examinations	Inadequate number of retinal examinations	p value
n (%)	185 (60.3%)	122 (39.7%)	
Type 1 diabetes Type 2 diabetes	134 (72.4%) 51 (27.6%)	74 (60.7%) 48 (39.3%)	
Age (years)	32.9 ± 5.3	31.5 ± 5.4	0.02
Gravida	2.4 ± 1.5	2.8 ± 2.2	0.16
Parity	0.9 ± 1.1	1.0 ± 1.3	0.13
Caucasian	174 (94.1%)	104 (85.2%)	0.01
Diabetes duration (years)	11.28 ± 5.68	9.25 ± 5.77	0.007
Non smokers	158 (85.4%)	110 (90.2%)	0.29
Attendance at Prepregnancy Care	108 (58.4%)	21 (17.2%)	<0.001
Folic acid	129 (69.7%)	66 (54.1%)	0.001
1st Trimester HbA1c mmol/mol (%)	55 ± 16 (7.2 ± 1.5)	54 ± 18 (7.1 ± 1.6)	0.47
3rd Trimester HbA1c mmol/mol (%)	45 ± 10 (6.3 ± 0.9)	46 ± 11 (6.4 ± 1.0)	0.43
Years 2006 - 2008	48 (25.9%)	84 (68.9%)	
Years 2009 - 2012	137 (74.1%)	38 (31.1%)	

Data are expressed as n(%) or mean ± standard deviation.

Table 4.3: Maternal Factors Associated with receiving Appropriate Retinal Evaluation during Pregnancy

	Odds Ratio	Confidence Interval	p value
Age	1.02	0.97 – 1.08	0.38
Ethnicity	0.71	0.27 – 1.85	0.48
Diabetes type	0.95	0.46 – 1.98	0.89
Diabetes Duration	1.03	0.99 – 1.07	0.15
Attendance at prepregnancy care	6.23	3.39 – 11.46	<0.001
Folic Acid Use	0.97	0.56 – 1.67	0.97

Table 4.4: Women who received Appropriate Screening (n=185). Characteristics of those who demonstrated Retinopathy Progression compared with those who did not

	No progression	Progression	p value
n (%)	137 (74.1%)	48 (25.9%)	
Diabetes Type 1 Diabetes Type 2	92 (67.2%) 45 (32.8%)	42 (87.5%) 6 (12.5%)	
Age (years)	32.64 ± 5.35	33.60 ± 5.15	0.28
White European	128 (93.4%)	46 (95.8%)	0.54
Parity	0.99 ± 1.16	0.73 ± 1.05	0.09
Gravida	2.44 ± 1.54	2.21 ± 1.53	0.17
Body Mass index (kg/m^2)	28.78 ± 6.32	27.50 ± 5.30	0.35
Prepregnancy care	82 (59.9%)	26 (54.2%)	0.49
Folic acid	97 (70.8%)	32 (66.7%)	0.59
Diabetes duration (years)	9.79 ± 8.36	14.43 ± 8.42	<0.001
Excessive weight gain in pregnancy	76 (55.5%)	29 (60.4%)	0.88
1st trimester HbA1c mmol/mol (%)	53 ± 15 (7.0 ± 1.4)	61 ± 17 (7.7 ± 1.6)	0.01
3rd trimester HbA1c mmol/mol (%)	45 ± 10 (6.3 ± 0.9)	45.0 ± 8 (6.3 ± 0.70)	0.89
Change in HbA1c between 1st and 3rd trimester mmol/mol (%)	8 ± 10 (0.7 ± 0.9)	15 ± 15 (1.38 ± 1.33)	0.004
Preeclampsia	17 (12.4%)	7 (14.6%)	0.80
Systolic blood pressure at booking (mmHg)	122.1 ± 13.0	128.6 ± 18.0	0.03
Diastolic blood pressure at booking (mmHg)	72.89 ± 10.3	76.0 ± 9.4	0.73
Non smoker	118 (86.1%)	40 (83.4%)	0.63
Baseline Findings:			
R0 (no retinopathy)	82 (59.9%)	32 (66.7%)	
R1 (background)	33 (24.1%)	9 (18.8%)	
R2 (pre-proliferative)	6 (4.4%)	4 (8.3%)	
R3 (proliferative)	10 (7.3%)	0 (0%)	
Maculopathy	6 (4.4%)	3 (6.3%)	

Data are expressed as n(%) or mean ± standard deviation.

Table 4.5: Factors Associated with Retinopathy Progression

	Odds Ratio	Confidence Interval	p value
Duration of diabetes	1.04	0.99 – 1.10	0.12
Diabetes type	0.47	0.15 – 1.54	0.21
1st trimester HbA1c	0.83	0.53 – 1.30	0.42
HbA1c reduction between 1st & 3rd trimester	2.05	1.09 – 3.87	0.03
Systolic blood pressure at booking	1.03	1.01 – 1.06	0.02

4.5 Discussion

4.5.1 Summary and Discussion of Findings

In an unselected population of women with pregestational diabetes, we demonstrate that 60.3% had an adequate number of ophthalmological examinations during pregnancy. Attendance at prepregnancy care was strongly associated with receiving adequate retinal evaluation in the subsequent pregnancy. Despite intensive glycaemic control and antihypertensive therapy as required, progression of retinopathy was observed in 14% of the total group and in 26% of those who had more than one retinal examination during pregnancy.

Recommendations for retinopathy screening and management in pregnancy vary significantly. The ADA advises *'an eye examination before pregnancy or in the 1st trimester, and then patients should be monitored every trimester and for one year post-partum as indicated by the degree of retinopathy and as recommended by the eye care provider'* [43]. NICE in the United Kingdom recommend retinal assessment following the 1st antenatal clinic appointment (unless they have had a retinal assessment in the last three months) and again at 28 weeks if the 1st assessment is normal. If any diabetic retinopathy is present, an additional retinal assessment should be performed at 16-20 weeks[42]. For the purposes of this study, we accepted a minimum of two retinal evaluations in separate trimesters in accordance with local guidelines[119]. Unfortunately, despite the existence of these guidelines, there was no retinal evaluation in 35% cases and just one evaluation in a further 9%. While many studies in the area of diabetic retinopathy in pregnancy include selected patients with complete ophthalmological evaluations only[59,169], a study of women with type 2 diabetes reported that only 73% had the available ophthalmological examinations[60]. In relation to this current study, there is not an automatic recall system for retinal evaluation in our antenatal centres and each woman must be referred individually. It our opinion that an automatic, standardized system of follow up as demonstrated by Hampshire et al would improve screening and follow up rates[163]. The majority of women who had just one eye examination were retinopathy free

and the lack of follow up in later pregnancy may reflect a perceived 'minimal risk' on behalf of the patient and health care provider with more focus being placed on those patients with established retinopathy.

Another interesting observation presented herein is the association between attendance at a prepregnancy care programme and adequate retinal assessment in the subsequent pregnancy. It is reasonable to assume that the educational component of the programme informs women on recommended intervals for ophthalmology review during pregnancy and these women are more likely to ensure they receive and attend appointments. The increased attendance at prepregnancy care undoubtedly explains the higher proportion of women taking prepregnancy folic acid in the group who received adequate eye assessments during pregnancy. Unfortunately we do not have information regarding the exact timing of prepregnancy care and levels of metabolic control and blood pressure at the time of attendance. Although there was no significant difference in progression of retinopathy between patients attending prepregnancy care and those who did not, improved metabolic control just before pregnancy may have influenced retinopathy progression during the subsequent pregnancy. Finally, the higher rates of adequate screening in the latter four years of the study reflect improvements in clinical care delivery as the Atlantic DIP programme became fully established.

This study highlights the on-going risk of retinopathy progression during pregnancy particularly among women with type 1 diabetes. Rasmussen et al evaluated 80 patients with type 2 diabetes and observed progression in 14%[60]. Vestgaard et al evaluated 102 women with type 1 diabetes and noted progression in 27%[89]. These studies did not find an association between glucose control and progression of retinopathy but this may be due to very tight prepregnancy glycaemic control or a type 2 error due to a lesser number of included subjects. However, our observations reinforce other published work that noted both significant and non-significant trends towards progression of retinopathy in the setting of a greater drop in HbA1c during the pregnancy[164,169,170]. While the 3rd trimester HbA1c was similar

between groups that did and did not progress in our study, the 1st trimester value was on average 8 mmol/mol (0.7%) higher in the group that developed retinopathy progression. The importance of prepregnancy glycaemic optimization should be highlighted as it is associated with a tendency toward less progression of retinopathy compared with waiting until pregnancy is confirmed in type 1 diabetes[60,169]. In the setting of an unplanned pregnancy with poor glycaemic control, the authors believe that glycaemic control should be prioritized and appropriately optimized as the long term consequences of poor glycaemic control during the pregnancy appear to outweigh those of retinopathy progression[169,171,172]. This issue has also received attention in studies involving a more general diabetes population. For example, although early worsening of diabetic retinopathy was noted in a higher proportion of those assigned to intensive treatment in the DCCT, the long-term benefits of intensive insulin treatment greatly outweighed the risks of this early worsening[173]. In our study the association between retinopathy progression and systolic blood pressure at booking is not unexpected as hypertensive disorders of pregnancy and indeed higher systolic blood pressure are factors known to negatively influence retinopathy [165,174,175].

In relation to the complication severity, two thirds of women who experienced retinopathy progression developed background retinopathy only and no women with a normal retinal examination during trimester one developed sight-threatening disease or required laser therapy. All women who developed sight-threatening disease had significant changes identified at baseline. These findings are reassuring, particularly as Hellstedt et al demonstrated a regression of mild retinopathy postpartum in a cohort of women with type 1 diabetes[176].

4.5.2 Strengths

Overall, this was a robust, nested cohort analysis performed retrospectively with data managed prospectively within the Atlantic-DIP database. We used robust statistical methods to evaluate rates of retinopathy progression and employed regression analysis to demonstrate factors associated with disease

progression and adequate retinal evaluation during pregnancy. Our patients and their management during pregnancy is a reflection of real-life clinical practice and includes patients with both type 1 and 2 diabetes mellitus and varying durations of disease. The findings are externally valid particularly in relation to other predominantly White European populations.

4.5.3 Limitations

The observational study design has inherent limitations including the potential influence of unmeasured covariates such as additional medications. A further limitation of the study is that we do not have postpartum evaluations to determine the longer-term progression of retinopathy. However, Arun et al studied women with type 1 diabetes for 5 years post delivery and concluded that pregnancy is not associated with post-partum worsening of retinopathy[171]. Additionally, in the Pittsburgh Epidemiology of Diabetes Complications Pregnancy Study, it was observed that the overall prevalence of retinopathy in women with prior pregnancy was similar to that of matched nulliparous women[172].

4.5.4 Conclusions

In summary, with the establishment of a structured antenatal care programme, more women are receiving an adequate number of retinal examinations during pregnancy. The introduction of an automatic recall system has the potential to improve service delivery. A significant proportion of women continues to experience deterioration in retinopathy during pregnancy validating the need for close follow up. Finally, the importance of prepregnancy care to fully inform women on the need for more frequent retinal assessment during pregnancy and allow preconceptual optimisation of glycaemic control and blood pressure should be emphasised. The results of this study will assist the health-care professional to design and provide high quality antenatal care for women with pregestational diabetes mellitus.

Chapter 5: A Regional Approach to Prepregnancy Care in Women with Type 1 and Type 2 Diabetes

A Prepregnancy Care Program for Women With Diabetes: Effective and Cost Saving.
Egan AM, Danyliv A, Carmody L, Kirwan B, Dunne FP.
J Clin Endocrinol Metab. 2016 Apr;101(4):1807-15.
(Reproduced with Permission – Appendix 3)

5.1 Introduction

Despite advances in clinical care, women with type 1 and type 2 diabetes continue to have an increased risk of serious adverse pregnancy outcomes[58,177,178]. The numbers of affected pregnancies are increasing, primarily due to the global rise in obesity, which frequently leads to type 2 diabetes[42]. Many adverse outcomes are associated with poor diabetes control in early pregnancy, highlighting the importance of pregnancy planning[42,72]. Prepregnancy care is the targeted support and additional clinical care offered to women planning pregnancy[67]. The value of a 'prepregnancy clinic' in reducing adverse outcomes was first demonstrated more than thirty years ago and specialised centres have since replicated these positive findings[73,107,109]. The effectiveness of a regional approach to prepregnancy care delivery was described in 2010[67].

Notwithstanding associated benefits, only a minority of women attend prepregnancy care. The CEMACH revealed that only 17% of maternity units in the United Kingdom offered prepregnancy care and just 10% women attended[65]. Although a co-ordinated, regionalised approach improved on these findings, despite increased counselling only 27% women participated[67]. Cited barriers to engaging with prepregnancy care include negative experiences with health professionals, lack of information and work commitments[82,83]. Furthermore, there exists a gap in the literature relating to the economic benefits of providing prepregnancy care, and this may act as a barrier to healthcare providers who wish to establish a service. The authors believe that evidence of a good financial return on the investment required to deliver prepregnancy care would have a strong influence on future resource allocation and lead to improved accessibility.

5.2 Study Objective

This study describes the development, implementation and evaluation of a regional prepregnancy care programme for women with type 1 and type 2 diabetes. A cost-analysis study will assess if the programme delivery is associated with a reduced cost of treating adverse pregnancy outcomes in the 1st year post delivery. We hypothesise that our prepregnancy care programme is associated with improved clinical outcomes and is cost effective.

5.3 Methods

5.3.1 Study Design

This prospective cohort study included 414 women with type 1 and type 2 diabetes attending antenatal centres along the Irish Atlantic Seaboard between January 2006 and December 2014. The HSE Research Ethics Committee provided ethical approval and women consented in writing to participation.

5.3.2 Prepregnancy Care Delivery

Referrals to the prepregnancy care programme were accepted from specialist providers, primary care clinicians and from women who self-referred. The programme was delivered using a standardized proforma according to principles laid out in NICE guidance[42]. It included patient education, a full medication review, assessment and treatment of diabetes complications and thyroid status, commencement of folic acid 5mg per day and a focus on intensive glucose monitoring with a target HbA1c of <43 mmol/mol (6.1%) preconception if feasible. A consultant endocrinologist based at the central hub travelled monthly to each of the other locations to support the local clinicians. A local endocrinologist, diabetes nurse specialist and dietician assisted with delivery of the programme locally and a centrally located coordinator monitored data collection for each site.

In 2006 at the time of programme initiation, specialists and general practitioners in the area were informed in writing and reminded of the service on a yearly basis. In 2010, in an effort to improve attendance, an information leaflet was also posted to all women of childbearing age with type 1 or 2 diabetes via a diabetes register. This was written in Plain English and emphasised the importance of pregnancy planning and attendance at prepregnancy care. Copies of this leaflet were also distributed to general practitioners and specialists and information posters provided for display in outpatient waiting areas. Information sessions for professionals were convened in the region and information about the service was disseminated via newspapers and radio. These activities were repeated on a yearly basis. Additionally in 2010, following qualitative research, the service became more personalised by providing flexible appointments via the central coordinator and ensuring a non-confrontational clinical environment with a focus on the positive aspects of pregnancy[83].

5.3.3 Definitions and Outcomes

Serious adverse outcomes comprise shoulder dystocia, congenital malformation, stillbirth or neonatal death. Shoulder dystocia is diagnosed and recorded by the delivering obstetrician when the foetal shoulders do not deliver after the head has emerged from the mother's introitus due to either one or both shoulders becoming impacted against the bones of the maternal pelvis. Congenital malformations are defined by the EUROCAT criteria[123]. Stillbirth is the delivery of a foetus showing no signs of life at ≥24 weeks' gestation. Neonatal death is the death of a live-born infant within the first 28 days of life. Miscarriage is the spontaneous loss of a foetus at <24 weeks' gestation. Prematurity is defined as delivery before 37 weeks gestation. Additional neonatal outcomes examined included LGA (≥90th centile by gestational age), macrosomia (birth weight ≥ 4.5 kg), and SGA (≤10th centile by gestational age)[122]. Gestational age was determined at the booking visit using obstetric ultrasound. Measured maternal outcomes included gestational hypertension (blood pressure

≥140/90 mm Hg on at least two occasions more than 6 hours apart in women with normal booking blood pressure), preeclampsia [hypertension, proteinuria (≥300 mg per 24 h) onset ≥ 20 weeks], and caesarean delivery. To calculate GWG, the difference between the 1st recorded weight in the 2nd trimester and the pre-delivery weight was measured. This was compared with IOM guidelines to assess whether the upper limit of recommended weight gain as per BMI category was breached according to previously described methodology (chapter 3; 3.3.2). Subsequently, women were categorized into one of two groups according to whether they demonstrated excessive or non-excessive GWG.

Maternal demographic and anthropometric data along with information on folic acid use, HbA1c and hypoglycaemia requiring hospital admission were recorded. Prepregnancy HbA1c refers to the HbA1c result at initiation of prepregnancy care among attenders and HbA1c six months prepregnancy in non-attenders.

5.3.4 Complication Costs

All the recorded complications that were deemed to have resource use implications in the 1st year post delivery entered the study. The cost elements were thus based on the health care utilization related to stillbirth, mode of delivery, NICU admission, maternal hypertensive disorders in pregnancy and surgeries in the 1st year of life required to treat congenital malformations. Each element of health care utilization was assigned a unit cost based on available estimates in 2014 Irish prices (table 5.1). The cost of stillbirth (€1,997.89 including bereavement and genetic post-mortem examinations) and hypertensive disorders (€7,964.71 including treatment, longer ante- and post-natal stay) were based on the international estimates and were inflated to 2014 prices using country specific Consumer Price Index (CPI) (health component if available) and, where international estimation used, transferred to Ireland using Purchase Power Parity indexes[179-182]. The cost of the mode of delivery, NICU stays, and malformations were based on the closest corresponding Diagnosis Related Group

(DRG) cost from the Irish Case-mix database and were inflated to 2014 prices using the health component of the CPI[183,184].

5.3.5 Cost of Delivery of Prepregnancy Care

Micro-costing was completed to define the cost of delivering prepregnancy care on a regional basis (table 5.2). The cost of the initial visit was estimated at €108.81 and included review by a consultant physician (15 minutes), dietician (20 minutes) and diabetes nurse specialist (15 minutes). Overheads (including administrative support) were also taken into account (25% of net labour) along with the cost of laboratory tests. Subsequent visits were costed at €51.76 and included consultant physician review (10 minutes), diabetes nurse specialist review (15 minutes), overheads (25% of labour) and assessment of HbA1c. During the study period, 224 women attended prepregnancy care and 148 became pregnant. The total cost of delivering the programme was €66,454.32 resulting in a cost of €449.02 per patient who became pregnant (or €269.67 per attendee) (table 5.3).

The expected reduction in cost per pregnancy for those who attended prepregnancy care was compared with the expected cost of delivering prepregnancy care to these women. The latter estimation included the cost of prepregnancy care provision to women who attended prepregnancy care during the same time period but did not become pregnant.

5.3.6 Data Management and Statistical Analysis

Collected data were prospectively recorded using an optimized digital database, namely DIAMOND (Hicom, Woking, UK). Hypothesis testing was performed on data of equal variance and normal distribution using an unpaired *t*-test. The Mann-Whitney test was used as the non-parametric alternative. A χ^2 analysis was used to compare sample proportions. Logistic regression was used for multivariate analyses. Data are expressed as n(%), means ± standard deviation of

the mean, aOR, and 95% CI. The difference between the total cost and individual components between the groups were assessed in univariate and multivariate analyses. For univariate cost analyses, a parametric t-test and non-parametric rank-sum test (for cross validation) were used. The adjusted difference in total cost was assessed in a multivariate regression model. Generalised linear regressions (GLM) with log link function and gamma distributed error terms were used for the analysis of the skewed estimates. The predictions, holding background characteristics at the average sample level, were used to assess the adjusted difference.

Statistical significance was accepted when the 95% CI did not contain one (regression analyses/ratios) or zero (multiple group comparisons/ means). The significance level was accepted when $\alpha<0.05$ for two-tailed analyses.

Table 5.1: Costing of Treatment of Complications

Cost item	Cost 2014 prices	Source	Assumptions
Miscarriage	€ -		Non-differentiated cost (assume similar rate in both groups)
Stillbirth/neonatal death	€ 1,997.89	[179]	United Kingdom: £1242 to £1804 in 2010 prices (bereavement and investigations)
Mode of delivery			
Normal vaginal	€ 2,341.87	[183]	
Instrumental	€ 3,239.13	[183]	weighted average for delivery with operative procedures
Elective caesarean	€ 4,818.22	[183]	uncomplicated caesarean delivery
Emergency caesarean	€ 6,255.09	[183]	complicated caesarean delivery
NICU stays			
preterm/premature	€ 15,071.41	[183]	weighted average for admission with low birth weight (<2.5kg); ALOS 18.01days
term babies	€ 2,905.66	[183]	weighted average for admission with normal birth weight (>=2.5kg); ALOS 3.83days
Hypoglycaemia	€ -	-	No effect apart from increased neonatal stay in premature babies
Hypertensive disorders of pregnancy (treatment)	€ 7,694.71	[180,181]	Non-differentiated cost (assume similar rate in both groups)
Polyhydramnios	€ -	-	No additional cost
Shoulder dystocia	€ -	-	No additional cost
Malformations			
Cardiac malformation	€ 83,070.52	[183]	Cardiothoracic/Vascular Procedures for Neonates (ALOS 34.24)
Oro-facial cleft	€ 10,355.38	[183]	Surgical Repair for Cleft Lip (ALOS 3.47)
Oesophageal atresia	€ 15,440.54	[183]	Neonatal admission with significant operative procedure No Multi Major Problems (ALOS 10.93)
Polydactaly	€ 3,214.50	[183]	Hand procedures, surgical inpatient (ALOS 1.3)

ALOS: average length of stay; NICU: neonatal intensive care unit

Table 5.2: Micro-costing: Assessing Cost of Prepregnancy Care Delivery

	Input	Unit cost Net	Unit cost Gross	Cost	Year	CPI	Cost 2014
Initial Visit							
Consultant	15 min	€122.17	€140.19	€35.05	2013	1.177	€41.25
Dietician	20 min	€35.76	€41.03	€13.68	2013	1.177	€16.10
Diabetes nurse specialist	15 min	€33.12	€38.01	€9.50	2013	1.177	€11.18
Overheads (25% of labour)				€12.69	2013	1.177	€14.93
Bloods							
Complete blood count	1		€4.04	€4.04	2013	1.177	€4.76
HbA1c	1		€3.95	€3.95	2013	1.177	€4.65
Liver function tests	1		€5.84	€5.84	2013	1.177	€6.87
Urea and creatinine	1		€3.53	€3.53	2013	1.177	€4.15
Thyroid function tests	1		€4.18	€4.18	2013	1.177	€4.92
Cost of initial visit							€108.81
Subsequent visit							
Consultant	10 min	€122.17	€140.19	€23.36	2013	1.177	€27.50
Diabetes nurse specialist	15 min	€33.12	€38.01	€9.50	2013	1.177	€11.18
Overheads (25% of labour)				€7.16	2013	1.177	€8.43
Bloods							
HbA1c			€3.95	€3.95	2013	1.177	€4.65
Cost of subsequent visit							€51.76

Table 5.3: Calculation of the Cost of Prepregnancy Care per Delivery (January 2006 – December 2014)

		All attending	Did not become pregnant	Became pregnant
n		224	76	148
Number of visits	mean	4.63	5.11	4.39
	std.err.	(4.11)	(3.58)	(4.35)
Cost of initial visit		€108.81		
Cost of subsequent visit		€51.76		
Cost of prepregnancy care	mean	296.67	321.30	284.02
	std.err.	(212.83)	(185.10)	(225.30)
Total cost of programme	cost*224	€66,454.32		
Cost per woman		**€296.67**		**€449.02**

Std err: standard error

5.4 Results

5.4.1 Patient Characteristics

In total, 414 pregnancies were included and 149 (36%) attended prepregnancy care. Between 2006 and 2009, 19% (36 of 186) attended prepregnancy care and following increased recruitment initiatives from 2010 onwards, there was a significant improvement with an average attendance of 50% (113 of 228) ($p<0.001$). There was an attendance of 41% among those with type 1 (111 of 269), and 26% among those with type 2 diabetes (38 of 146) ($p=0.002$). The cohort of women who received prepregnancy care differed from those who did not by several characteristics (table 5.4). Those who attended were older (33.8 versus 31.9 years, $p<0.001$), had a longer duration of diabetes (11.7 versus 9.5 years), a lower HbA1c [57 versus 65 mmol/mol (7.4 versus 8.1%), $p=0.002$) and a higher proportion were nulliparous (45.0 versus 38.9%, $p=0.001$). Women who attended were more likely to have preconception folic acid (5mg per day) (97.3 versus 57.7%, $p<0.001$), report a non-smoking status at booking antenatal visit (91.3 versus 83.4%, $p=0.03$) and less likely to be receiving a potentially harmful medication at conception (0.7 versus 6.0%, $p=0.008$). Attendees had a significantly lower 1st trimester HbA1c [51 versus 60 mmol/mol (6.8 versus 7.6%), $p<0.001$) and their HbA1c measurements remained significantly lower throughout the entire pregnancy. A higher proportion of attendees achieved the target HbA1c of <43 mmol/mol (6.1%) in the 1st trimester (24.4 versus 13.6%, $p=0.006$). Examining the less stringent goal of HbA1c <48 mmol/mol (6.5%) in the 1st trimester, 36.2% of attendees versus 23% of non-attendees reached this target ($p=0.004$). There were no instances of severe hypoglycaemia requiring hospital admission during the study period.

5.4.2 Maternal and Neonatal Outcomes

Rates of maternal complications including gestational hypertension and preeclampsia were similar between both groups (table 5.5). While there was no difference in overall rates of caesarean delivery between

groups (68.6 versus 62.0%, p=0.22), those that attended prepregnancy care had a higher rate of elective caesarean delivery (45.2 versus 32.8%, p = 0.02) with a non-significant reduction in rates of emergency caesarean delivery (23.4 versus 29.3%, p=0.23). The percentage of live births and miscarriages were similar between both groups (table 5.5). Congenital malformations were lower (0.8 versus 5.2%, p=0.04) and there were fewer serious adverse outcomes (2.4 versus 10.5%, p=0.007) among attendees. Among the live-born infants (n=343), there were lower rates of NICU admissions among offspring of women who attended prepregnancy care (44.3 versus 62.0%, p=0.002). Table 5.6 outlines potential independent predictors of serious adverse outcome in women with type 1 and type 2 diabetes. Attendance at prepregnancy care was associated with a reduced risk of serious adverse outcome (odds ratio 0.26, 95% CI 0.07 – 0.77, p=0.04). Other potential factors were not significant.

5.4.3 Type 1 and type 2 Diabetes

Women with type 1 and type 2 diabetes were examined independently to assess for within group differences (tables 5.7 and 5.8). Women with type 1 diabetes attending the programme were better prepared for pregnancy but only a minority achieved a 1st trimester HbA1c of <43 mmol/mol (6.1%) (12.6% of attenders versus 7.6% of non-attenders, p=0.007). Offspring had lower rates of serious adverse outcome (1.8 versus 11.4%, p=0.003). Additionally, a lower rate of neonatal hypoglycaemia (11.7 versus 23.4%, p=0.02) was recorded and NICU admissions were less frequent (47.7% versus 74.2%, p<0.001) among offspring of attendees. There was a higher rate of excessive maternal GWG among those who attended prepregnancy care (37.7 versus 24.7%, p=0.03).

The overall number of women with type 2 diabetes attending prepregnancy care was low (38 of 146, 26.2%), especially among those of non-white ethnicity (6 of 41, 14.6%). Attendees had higher rates of preconception folic acid use (94.7 versus 55.1%, p<0.001) and

a greater number achieved the target HbA1c of <43 mmol/mol (6.1%) (58.0 versus 22.4%, p<0.001).

5.4.4 Cost Analysis

Table 5.9 describes the difference in total complication costs and individual components between those who attended prepregnancy care versus usual antenatal care only. The average total cost of complications per pregnancy attending prepregnancy care is €3,251.10 less than the cost for those receiving usual care only and the difference is significant (t-test: p = 0.001; rank-sum: p=0.01). The main major component of the difference is the cost associated with malformations - €1,990.32 per delivery in the usual care group compared with no observed cost in the prepregnancy care group (t-test: p=0.01; rank-sum: p=0.02). The next major component is NICU admissions which account for a significant between-group difference of €749.83 (t-test: p=0.04, rank-sum: p=0.003). The costs associated with mode of delivery, stillbirths and hypertensive disorders are lower for those attending prepregnancy care but the difference is not significant. A multivariate regression analysis of total cost is detailed in table 5.10. Attendance at prepregnancy care is the only factor significantly associated with a cost reduction (coefficient -0.3, p=0.03). Maternal obesity, smoking, non-white ethnicity, and age have a cost-increasing effect but do not reach significance (coefficients: 0.29, p=0.08; 0.03, p=0.89; 0.17, p=0.46; and 0.01, p=0.66 respectively). The adjusted difference in complication costs between those who received prepregnancy care versus usual care remains substantial (usual care: €9,829.87, prepregnancy care: €7,252.17, difference: -€2,577.70). This difference offsets the per pregnancy cost of delivering prepregnancy care (€449.02).

Table 5.4: Characteristics of Women According to Prepregnancy Care Attendance (n=414)

	Prepregnancy Care n=149 (36%)	No prepregnancy care n=265 (64%)	p-value
Type 1 diabetes	111 (74.5)	158 (59.6)	
Type 2 diabetes	38 (25.5)	107 (40.4)	0.002
Number of visits to prepregnancy care	4.4 (4.4)	n/a	n/a
Diabetes duration (years)	11.7 ± 9.7	9.5 ± 8.7	0.02
Maternal complications			
Retinopathy	59 (39.6)	107 (40.4)	0.87
Nephropathy	15 (10.1)	29 (10.9)	0.78
Neuropathy	4 (2.6)	7 (2.6)	1.00
Ethnicity			
white	143 (96.0)	229 (86.4)	0.003
other	6 (4.0)	36 (13.6)	
Age (years)	33.8 ± 4.6	31.9 ± 5.7	<0.001
Parity	0.72 (0.81)	1.2 (1.3)	<0.001
Nulliparous	67 (45.0)	103 (38.9)	0.001
Smoking status at booking			
Current smoker	13 (8.7)	44 (16.6)	0.03
Non-smoker	136 (91.3)	221 (83.4)	
Preconception folic acid	145 (97.3)	153 (57.7)	<0.001
Teratogenic medications at conception	1 (0.7)	16 (6.0)	0.008
BMI at booking (kg/m^2)	28.3 ± 5.6	29.4 ± 6.9	0.09
BMI Category			
Normal (≤ $24.9kg/m^2$)	46 (30.9)	82 (32.0)	
Overweight (25-$29.9kg/m^2$)	52 (34.9)	73 (28.5)	
Obese (≥ $30.0kg/m^2$)	51 (34.2)	101 (39.5)	0.37
Booking blood pressure			
Systolic	122.9 ± 12.5	123.7 ± 16.2	0.56
Diastolic	74.5 ± 8.5	73.0 ± 10.0	0.11
Glycaemic control			
Prepregnancy HbA1c mmol/mol (%)	57 ± 14 (7.4 ± 1.3)	65 ± 27 (8.1 ± 2.5)	0.002
1^{st} trimester HbA1c<6.5%	54 (36.2)	61 (23.0)	0.004
1^{st} trimester HbA1c<6.1%	36 (24.2)	36 (13.6)	0.006
1^{st} timester HbA1c mmol/mol (%)	51 ± 13 (6.8 ± 1.2)	61 ± 20 (7.7 ± 1.8)	<0.001
2^{nd} trimester HbA1c mmol/mol (%)	44 ± 8 (6.2 ± 0.7)	49 ± 12 (6.6 ± 1.1)	<0.001
3^{rd} trimester HbA1c mmol/mol(%)	43 ± 8 (6.1 ± 0.7)	48 ± 11 (6.5 ± 1.0)	0.001
Insulin therapy during pregnancy	146 (98.0)	243 (91.7)	0.009

Data are expressed as n(%) or mean ± standard deviation.
BMI: body mass index.

Table 5.5: Pregnancy Outcomes According to Prepregnancy Care Attendance (n=414)

	Prepregnancy Care n=149	No prepregnancy care n=265	p-value
Pregnancy Outcome			
Livebirth	122 (81.9)	221 (83.4)	
Miscarriage	25 (16.8)	36 (13.6)	
Stillbirth	2 (1.3)	8 (3.0)	
Neonatal death	0	0	0.41
Maternal complications			
Hypertension	25 (16.8)	54 (20.4)	0.37
Preeclampsia	13 (8.7)	28 (10.5)	0.54
Delivery[1]	n=124	n=229	
Age at delivery (weeks)	38.0 ± 2.8	37.9 ± 2.8	0.68
Prematurity			
<37 weeks	17 (11.4)	47 (17.7)	0.09
<34 weeks	8 (6.5)	22 (9.6)	0.31
Normal vaginal delivery[2]	28 (22.6)	61 (26.6)	0.40
Instrumental delivery	11 (8.9)	26 (11.4)	0.47
Caesarean delivery	85 (68.6)	142 (62.0)	0.22
Elective Caesarean	56 (45.2)	75 (32.8)	0.02
Emergency Caesarean	29 (23.4)	67 (29.3)	0.23
Neonatal complications			
Serious adverse outcome	3 (2.4)	24 (10.5)	0.007
Shoulder dystocia	0	6 (2.6)	0.07
Hypoglycaemia	15 (12.1)	22 (19.2)	0.09
Congenital malformation	1 (0.8)	12 (5.2)	0.04
Cardiac	0	7 (58.3)	
Digestive System	0	1 (8.3)	
Limb	0	1 (8.3)	
Nervous System	0	2 (16.6)	
Oro-facial Clefts	0	1 (8.3)	
Other anomalies / syndromes	1 (100)	0	
Birthweight (kg)	3.6 ± 0.9	3.5 ± 0.8	0.13
Large for gestational age	38 (30.7)	58 (25.9)	0.34
Small for gestational age	5 (4.0)	20 (8.9)	0.09
Macrosomia	11 (8.9)	17 (7.7)	0.70
Excessive gestational weight gain	61 (50)	80 (39.4)	0.06
Neonatal care[3]	n=122	n=221	
NICU	54 (44.3)	137 (62.0)	
Postnatal ward	68 (55.7)	84 (38.0)	0.002

Data are expressed as n(%) or mean ± standard deviation.
[1]All pregnancies after 20 weeks gestation. [2]Excluding instrumental deliveries. [3]All livebirths.
NICU: neonatal intensive care unit.

Table 5.6: Independent Predictors of Serious Adverse Pregnancy Outcome

Variable	Odds Ratio	95% Confidence Interval	p-value
Age (years)[1]	0.95	0.855 – 0.262	0.26
Duration of diabetes (years)[1]	1.04	0.970 – 1.111	0.28
1st Trimester HbA1c (%)[2]	0.99	0.735 – 1.335	0.95
Prepregnancy care attendance[3]	0.26	0.068 – 0.966	0.04
Parity[4]	1.20	0.810 – 1.769	0.37
BMI at booking (kg/m^2)	1.02	0.932 – 1.118	0.66
Smoking	1.78	0.546 – 5.811	0.34
Type 1 diabetes	1.86	0.314 – 11.060	0.49
Other ethnicity	1.81	0.159 – 20.433	0.63

[1]Change in risk per year increase in age / duration of diabetes. [2]Increase in risk for each 1% increase in HbA1c. [3]Decrease in risk for those who attended prepregnancy care versus those who did not. [4]Increase in risk per unit increase in parity. BMI: body mass index.

Table 5.7: Characteristics of Women with Type 1 Diabetes and Type 2 Diabetes According to Prepregnancy Care Attendance

	Type 1 Diabetes (n=269)			Type 2 diabetes (n=146)		
	Pre-pregnancy Care n=111 (41.3%)	**No pre-pregnancy care n=158 (58.7%)**	**p-value**	**Pre-pregnancy Care n=38 (26.2%)**	**No pre-pregnancy care n=107 (73.8%)**	**p-value**
Number of visits to prepregnancy care	4.7 ± 4.7	n/a	n/a	3.4 ± 2.8	n/a	n/a
Duration of diabetes (years)	14.7 ± 9.4	14.0 ± 8.0	0.48	2.8 ± 2.5	2.8 ± 4.3	1.00
Maternal complications						
Retinopathy	53 (47.7)	90 (57.0)	0.14	6 (15.8)	17 (15.9)	0.99
Nephropathy	15 (13.5)	23 (14.6)	0.80	0	6 (5.6)	0.34
Neuropathy	4 (3.6)	6 (3.8)	1.00	0	1 (0.9)	1.00
Ethnicity						
White	111 (100)	157 (99.4)		32 (84.2)	72 (67.3)	
Other	0	1 (0.6)	1.00	6 (15.8)	35 (32.7)	0.04
Age (years)	34.0 ± 4.9	30.7 ± 5.7	<0.001	33.3 ± 3.5	33.7 ± 5.3	0.59
Parity	0.7 ± 0.8	0.9 ± 1.1	0.02	1.0 ± 0.9	1.5 ±1.6	0.01
Nulliparous	56 (50.5)	71 (44.9)	0.37	11 (28.9)	32 (29.9)	0.91
Smoking status						
Current smoker	8 (7.2)	33 (21.0)		5 (13.2)	11 (10.3)	
Non-smoker	103 (92.8)	125 (79.0)	0.002	33 (86.8)	96 (89.7)	0.63
Preconception folic acid	109 (98.1)	94 (59.5)	<0.001	36 (94.7)	59 (55.1)	<0.001
Teratogenic medications at conception	1 (0.9)	15 (9.5)	0.003	0	1 (0.9)	1.00
BMI at booking (kg/m^2)	26.5 ± 4.2	26.4 ± 4.9	0.86	33.6 ± 5.8	33.7 ± 7.1	0.93
BMI Category						
Normal (≤24.9kg/m^2)	43 (38.7)	70 (44.3)		3 (7.9)	12 (11.2)	
Overweight (25-29.9kg/m^2)	46 (41.4)	48 (30.4)		6 (15.8)	25 (23.3)	
Obese (≥ 30.0kg/m^2)	22 (19.8)	33 (20.9)	0.27	29 (76.3)	68 (63.6)	0.43
Booking blood pressure						
Systolic	122.9 ± 12.9	121.2 ± 15.8	0.36	122.8 ± 11.5	127.3 ± 16.2	0.12
Diastolic	74.1 ± 8.3	71.5 ± 9.2	0.02	75.6 ± 9.1	75.1 ± 10.8	0.81
Glycaemic control						
1st trimester						
HbA1c: <6.5%	31 (27.9)	22 (13.9)	0.007	23 (60.5)	39 (36.4)	0.02
<6.1%	14 (12.6)	12 (7.6)	0.17	22 (58.0)	24 (22.4)	<0.001
1st timester HbA1c	6.9 ± 1.0	8.1 ± 1.7	<0.001	6.3 ± 1.5	7.0 ± 1.7	0.05
2nd trimester HbA1c	6.3 ± 0.8	6.9 ± 1.2	<0.001	5.7 ± 0.5	6.1 ± 0.7	0.002
3rd trimester HbA1c	6.2 ± 0.7	6.7 ± 1.1	<0.001	5.9 ± 0.6	6.1 ± 0.8	0.22
Insulin therapy during pregnancy	111 (100)	158 (100)	n/a	35 (92.1)	85 (79.4)	0.08

Data are expressed as n(%) or mean ± standard deviation.
BMI: body mass index.

Table 5.8: Pregnancy Outcomes for Women with Type 1 Diabetes According to Prepregnancy Care Attendance

	Type 1 Diabetes (n=269)			Type 2 diabetes (n=146)		
	Pre-pregnancy Care n=111 (41.3%)	**No pre-pregnancy care n=158 (58.7%)**	**p-value**	**Pre-pregnancy Care n=38 (26.2%)**	**No pre-pregnancy care n=107 (73.8%)**	**p-value**
Pregnancy Outcome						
Livebirth	88 (79.3)	128 (81.0)		34 (89.5)	93 (86.9)	
Miscarriage	21 (18.9)	24 (15.2)		4 (10.5)	12 (11.2)	
Stillbirth	2 (1.8)	6 (3.8)		0	2 (1.9)	
Neonatal death	0	0	0.49	0	0	0.69
Maternal complications						
Hypertension	19 (17.1)	29 (18.4)	0.79	6 (15.8)	28 (26.2)	0.20
Preeclampsia	11 (9.9)	18 (11.4)	0.70	2 (5.3)	10 (9.3)	0.43
Delivery[1]	n=90	n=134		n=34	n=95	
Age at delivery (weeks)	37.9 ± 2.7	37.4 ± 3.0	0.23	38.4 ± 3.0	38.6 ± 2.2	0.69
Prematurity						
<37 weeks	12 (10.8)	35 (22.2)	0.02	5 (13.2)	12 (11.2)	0.75
<34 weeks	5 (5.6)	16 (11.9)	0.11	3 (8.8)	6 (6.3)	0.70
Normal Vaginal delivery[2]	20 (18.0)	27 (17.1)	0.04	8 (21.1)	33 (34.7)	0.55
Instrumental delivery	9 (8.1)	15 (9.5)	0.95	2 (5.9)	12 (12.6)	0.45
Caesarean delivery	61 (55.0)	92 (58.2)	0.89	24 (70.6)	50 (52.6)	0.07
Elective ceasarean	39 (35.1)	47 (29.7)	0.27	17 (50.0)	28 (29.5)	0.05
Emergency caesarean	22 (19.8)	45 (28.5)	0.14	7 (20.6)	22 (23.2)	0.95
Neonatal complications						
Serious adverse outcome	2 (1.8)	18 (11.4)	0.003	1 (2.9)	6 (6.3)	0.68
Shoulder dystocia	0	4 (2.5)	0.15	0	2 (2.1)	1.00
Congenital malformation	0	10 (6.3)	0.007	1 (2.9)	2 (2.1)	1.00
hypoglycaemia	13 (11.7)	37 (23.4)	0.02	2 (5.9)	7 (7.4)	1.00
Birth weight	3.6 ± 0.8	3.4 ± 0.81	0.07	3.5 ± 0.9	3.5 ± 0.8	0.97
Large for gestational age	27 (24.3)	38 (24.0)	0.91	11 (32.4)	20 (21.1)	0.28
Small for gestational age	2 (1.8)	12 (7.6)	0.05	3 (8.8)	8 (8.4)	0.94
Macrosomia	8 (7.2)	7 (4.4)	0.33	9 (26.5)	19 (20.0)	0.45
Excessive gestational weight gain	43 (38.7)	39 (24.7)	0.03	18 (52.9)	41 (43.2)	0.60
Neonatal care[3]	n= 88	n=128		n=34	n=93	
Postnatal ward	46 (52.3)	33 (25.8)		22 (64.7)	51 (54.8)	
Neonatal intensive care	42 (47.7)	95 (74.2)	<0.001	12 (35.3)	42 (45.2)	0.32

Data are expressed as n(%) or mean ± standard deviation.
[1]All pregnancies after 20 weeks gestation. [2]Excluding instrumental deliveries. [3]All livebirths.

Table 5.9: The Difference in Cost of Care and its Components between those who Received Usual Obstetric Care versus those who Attended Prepregnancy Care

		Group mean			p-value	
		Usual care (€)	PPC (€)	Diff. (€)	t-test	rank-sum
n		265	149	414		
Total Cost	mean	10,055.76	6,804.66	-3,251.10	0.001	0.01
	(std.err.)	(874.34)	(480.67)	(1,220.96)		
Stillbirth	mean	59.71	26.55	-33.16	0.24	0.29
	(std.err.)	(20.83)	(18.71)	(31.13)		
Mode of delivery	mean	3,802.00	3,707.52	-94.47	0.66	0.65
	(std.err.)	(127.61)	(172.42)	(213.72)		
Neonatal intensive care admission	mean	2,374.43	1,624.60	-749.83	0.04	0.003
	(std.err.)	(233.61)	(268.82)	(371.11)		
Hypertensive disorders	mean	1,829.31	1,445.99	-383.32	0.23	0.24
	(std.err.)	(201.60)	(247.09)	(326.53)		
Malformations	mean	1,990.32	0.00	-1,990.32	0.01	0.02
	(std.err.)	(762.83)	(0.00)	(1,017.86)		

PPC: prepregnancy care; Std. err: standard error.

Table 5.10: Multivariate Regression Analysis of the Total Cost: Generalised Linear Modelling with Log Link and Gamma Distributed Error Term.

	Coefficient	P-value
Prepregnancy care	-0.30	0.03
Age	0.01	0.66
Type 2 diabetes	-0.25	0.11
White ethnicity	-0.17	0.46
Smoker	0.03	0.89
BMI (overweight)	0.08	0.61
BMI(obese)	0.29	0.08
Parity (1)	-0.21	0.13
Parity (<1)	-0.17	0.32
AIC	20.17	
BIC	-2159.75	
Log likelihood	-4070.47	
Predicted cost		
Usual care	€9,829.87	
Prepregnancy Care	€7,252.17	
Difference	-€2,577.70	

AIC: Akaike's Information Criterion; BIC: Baysian Information Criterion; BMI: body mass index

Discussion 5.5

5.5.1 Summary and Discussion of Findings

This study describes and evaluates a regional prepregnancy care programme for women with type 1 and type 2 diabetes. The programme was co-ordinated centrally and delivered locally to bring the expertise to the individual, maximise uptake and improve pregnancy outcomes. This novel model of care delivery was revealed to be effective over nine years, was available to all women with diabetes in the region and will continue as routine care. We demonstrate a reduced risk of adverse pregnancy events among attendees and uptake was enhanced from 19% to 50% by increasing awareness among stakeholders. Our cost-analysis indicates that the average adjusted cost of treating adverse pregnancy outcomes is €2,578 less for those women who attend prepregnancy care. This fully offsets the average cost of prepregnancy care delivery which is estimated at €449 per pregnancy – a figure which also takes into consideration the cost of treating those women who attend the programme but do not become pregnant.

The overall uptake of 36% is an improvement on the only previously published regional programme that reported an attendance rate of 27% and we believe that regular, personalised contact with women and local clinicians had a favourable effect[67]. Furthermore, in delivering the programme, care was taken to address barriers to engagement identified in prior qualitative studies[82,83]. The appointment of a central coordinator further bolstered our attendance rates, an intervention noted to improve service engagement in our population of women with GDM[185]. While our attendance now approximates the proportion of planned pregnancies in the United Kingdom[67,186], there is progress to be made before we are level with other European countries where over 80% pregnancies in women with type 1 diabetes are planned[113]. In particular, women with type 2 diabetes, ethnic minorities and those with poor glycaemic control were

less likely to attend. There exists a challenge to design future recruitment strategies to incorporate these women and provide care to those who need it most.

Attendees were better prepared for pregnancy and their offspring experienced a lower rate of congenital anomalies and serious adverse outcomes along with reduced admissions to the NICU. Indeed, prepregnancy care attendance was the only significant factor independently associated with a reduction in a serious adverse pregnancy outcome. Although the value of prepregnancy care in women with type 2 diabetes is less well established, our findings are encouraging with significantly higher rates of pre-conceptual folic acid use and improved glycaemic control during the ensuing pregnancy. Our data reveal we are not meeting the NICE HbA1c target in many women with diabetes who are planning pregnancy. This target was recently raised from 43 to 48 mmol/mol (6.1% to 6.5%) but remains challenging to achieve, particularly in the setting of type 1 diabetes given the greater risk of hypoglycaemia[42]. Moving forward, there is evidence that the application of novel technologies may improve glycaemic control. An international Continuous Glucose Monitoring in Women with Type 1 Diabetes in Pregnancy Trial (CONCEPTT) is currently evaluating the role of real-time continuous glucose monitoring before and during pregnancy, and studies using closed-loop insulin delivery also hold promise for women with type 1 diabetes[126,187].

There were higher rates of excessive GWG among women with type 1 diabetes attending the prepregnancy care programme. This is an independent risk factor for increased offspring birth weight and identifies a need to give added attention to weight management while delivering prepregnancy care[86,188]. Although it is not clear why a greater proportion of attendees gained excessive weight in the subsequent pregnancy, increased weight gain was noted in previous trials of intensive insulin therapy[189]. One possibility is that the strong

focus on glycaemic control may have led to insulin-induced hypoglycaemia requiring additional caloric intake.

The primary cost saving results from a reduction in the frequency of congenital anomalies requiring early surgical intervention in the group that attended prepregnancy care. Although prior work in this field is limited, one study in the United States estimated net savings of $1,720.00 (€1,524.79) per enrolee in prepregnancy care over those who received prenatal care only[190]. However this study was published over 20 years ago and relied on retrospective, secondary data. A recent publication predicted that universal prepregnancy care would result in a lifetime societal cost saving of up to $5.5 billion (€4.9 billion) but again analyses were based on secondary data some of which was over 20 years old[191]. The latter issue is particularly relevant as it is unclear how improved obstetric care in recent years may attenuate potential savings. Furthermore, previous authors did not consider the cost of delivering prepregnancy care and while universal prepregnancy care is ideal, approximately 50% of pregnancies are unplanned making attendance at prepregnancy care unlikely for this group[186,192]. This current study addresses these limitations as our costings are based on prospectively collected data over a contemporary, nine-year period and more accurately reflect the real-life economic implications of providing prepregnancy care across a region. This information is particularly useful to health care providers aiming to assess the costs prior to establishing a prepregnancy care programme and may encourage third-party payers to realise cost-savings by reimbursing preconception care.

5.5.2 Strengths

As a randomized trial in this area would not be considered ethical[67], we completed a prospective observational cohort study and used robust statistical methods to evaluate differences in characteristics and pregnancy outcomes between groups. Our study contains detailed patient-level data, with the exception of socioeconomic status as

measurement is difficult in the context of the mixed urban-rural characteristics of the population.

5.5.3 Limitations

As there are baseline differences between women who did and did not attend the programme, characteristics of non-attenders may limit generalizability of clinical benefits to this group.

Limitations of the cost-savings analysis include generalizability to alternative healthcare delivery systems and patient populations. The increased marginal cost of recruiting non-attendees and designing a programme that overcomes the barriers within this group cannot be estimated. While there are differences between women with type 1 and 2 diabetes, these women were managed in the same prepregnancy care programme and so the cost analysis encompassed both groups. Finally, this study focused primarily on direct medical costs, however the true benefits of prepregnancy care extend beyond this estimation and include effects on quality of life and productivity. As a result of not including indirect costs, we have likely underestimated the overall impact of prepregnancy care.

5.5.4 Conclusions

In summary, a regional prepregnancy care programme is feasible, acceptable and is associated with improved pregnancy preparation and a significant reduction in adverse pregnancy outcomes for women with diabetes. The cost of running the programme is less than the immediate excess cost of complication management for those who do not attend prepregnancy care. These data support a global move towards provision of prepregnancy care for all women with diabetes of childbearing age and we provide an adaptable template for delivery of this care.

Chapter 6: A Study Protocol for a Core Outcome Set (COS) for Studies Evaluating Prepregnancy Care for Women with Diabetes.

Effectiveness of prepregnancy care for women with pregestational diabetes mellitus: protocol for a systematic review of the literature and identification of a core outcomes set using a Delphi survey.
Egan AM, Smith V, Devane D, Dunne FP.
Trials. 2015 Aug 14;16:356
(Open Access Article)

6.1 Introduction

Despite modern approaches to diabetes care, pregnancy can pose significant risk to both mother and infant in the presence of type 1 or type 2 diabetes, also described as pregestational diabetes [193]. Women with pregnancy complicated by diabetes have increased rates of adverse pregnancy outcomes including a congenital malformation rate twice that of the general maternity population, a fivefold increased risk of stillbirth and a threefold increased risk of perinatal mortality[57,58]. The caesarean rate for women with diabetes in pregnancy is 67% compared to 22% in the background population and rates of macrosomia are approximately 21% compared to 11% in the general maternity population[57,58,118,194].

The provision of structured clinical care before pregnancy, however, is associated with improved outcomes[67,109]. This is particularly true for rates of malformations and perinatal mortality as these are related to a greater extent to poor glycaemic control in early rather than later pregnancy[72]. The mechanism of this relationship is clear when one considers that foetal organogenesis is essentially completed by 7 weeks gestation, often before the woman knows she is pregnant[88]. It is recommended therefore that all women of reproductive age with diabetes be offered annual preconception counselling and advised to avoid unplanned pregnancy[42,67]. Prepregnancy care is the targeted support and additional care offered to women who are actually planning pregnancy[67]. Once women are ready to engage with prepregnancy care, they are reviewed at 1-3 monthly intervals by a multidisciplinary team. This team typically includes a diabetes physician, diabetes nurse/midwife specialist and dietician. Women will have a full medication review, reviews of diabetes related complications, assessment for other conditions more commonly associated with diabetes e.g. thyroid and coeliac disease and

commence folic acid. Diabetes-related complications and thyroid status will be assessed and glycaemic control optimized. It is recommended that the HbA1c level should be below 48mmol/mol (6.5%) if achievable without causing problematic hypoglycaemia[42]. There is not, however, an agreed standardised approach for provision of this care and while many groups have reported positive benefits associated with their own prepregnancy programmes, outcome reporting is varied and diverse[67,73,109].

Clinical studies should have defined outcomes that answer questions generated by the main hypothesis[195]. The outcomes potentially relevant to prepregnancy care programmes are diverse and include both maternal and foetal outcomes. Unfortunately, there is significant heterogeneity in the outcomes measured and reported in studies evaluating the effects of prepregnancy care for women with pregestational diabetes. This is highlighted in a systematic review and meta-analysis by Wahabi et al, which noted that of 21 included studies, only 13 included congenital malformations as an outcome of prepregnancy care and only 5 studies included the difference in the level of HbA1c[81]. This inconsistency in outcomes between studies makes meaningful comparison difficult and limits the ability to combine individual studies' findings into summary estimates. Further concerns include non-uniform outcome selection and reporting bias in clinical studies. These issues involve researchers selecting outcomes that suit their needs and reporting only favourable results [196,197]. To further highlight this issue, a recent descriptive survey of 6127 outcomes in 788 Cochrane reviews found that 37% of prespecified outcomes were not actually reported[198]. If study findings are to influence policy and practice then the chosen outcomes need to be relevant and important to key stakeholders to facilitate development of high quality care[196]. A Cochrane review[199] could identify only one randomised controlled trial evaluating different models of prepregnancy care for women with diabetes[200]. The authors recommended strongly the need for further large, high-quality

randomised controlled trials to evaluate the effect of different protocols of preconception care for women with pre-existing diabetes[199]. There is a risk that due to lack of guidance on appropriate outcomes, the usefulness of this future research in informing clinical practice will be limited.

One method of addressing this lack of uniformity is through the development, use and reporting of an agreed set of outcomes, known as a COS. The expectation is that the COS will always be collected and reported in all clinical trials, audits of practice and other forms of research that involve a specific clinical condition[196]. This will facilitate comparing and contrasting of studies and allow for combining of appropriate studies. The development of such COS is facilitated and supported by the COMET (Core Outcome Measures in Effectiveness Trials) Initiative, which was launched in 2010 and brings together interested researchers while minimising duplication of effort[196,201]. Importantly, a COS does not restrict researchers from evaluating additional outcomes, but rather represents a minimum that should be collected and reported. COS are now developed for many aspects of patient care and in 2014 the editors of over 50 journals initiated the CROWN (CoRe Outcomes in WomeN's Health) Initiative[202-205]. This has a number of aims, which include encouraging researchers to develop COS in the field of women's health, organising robust peer-review and facilitating effective dissemination of manuscripts [202].

6.2 Study Objective

In this paper we present a protocol for a study to develop a COS for trials and other studies evaluating the effectiveness of prepregnancy care for women with pregestational diabetes mellitus.

We describe in detail the following steps necessary to develop the COS:

(i) A systematic literature review to identify outcomes reported in studies evaluating prepregnancy care for women with pregestational diabetes.

(ii) Prioritisation of these outcomes from the perspective of key stakeholders including women with pregestational diabetes and clinicians, using a Delphi survey and consensus meeting.

6.3 Methods

6.3.1 Ethics

Ethical approval to conduct this study was sought and obtained from the ethics committee at Galway University Hospitals (home institution of the study's principal investigator).

6.3.2. Part 1: Generation of a List Containing Possible Relevant Outcomes via a Systematic Review.

6.3.2.1 Systematic Review Question

What are the outcomes reported in studies assessing the effectiveness of prepregnancy care for women with pregestational diabetes?

6.3.2.2. Systematic Review Method

Using a comprehensive search strategy, the following databases will be searched for relevant studies: Medical Literature Analysis and Retrieval System Online (MEDLINE), Exerpta Medica Database (EMBASE), WEB OF SCIENCE, Cochrane Library and the Cumulative Index to Nursing and Allied Health Literature (CINHAL). Clinicaltrials.gov will also be searched for relevant, ongoing trials. Key terms to guide the search will include "diabetes", "pregnancy", "prepregnancy",

"pre-pregnancy", "preconception" and "pre-conception", combined as appropriate using the Boolean operands 'AND' and 'OR'. Figure 6.1 outlines the detailed search strategies and time limits applied to each of the databases. The reference lists of all relevant studies will be searched for additional, relevant studies not retrieved by the electronic database search. Language restrictions will not be applied to the search strategy; however, selection of relevant papers will be restricted to English language publications. Searching all languages will enable us to identify the extent of potentially eligible additional papers that will not be included and consider if this presents a source of language bias.

6.3.2.3 Types of Studies

For the purpose of this phase of the development of the COS, we will include prospective cohort studies; case controlled trials; randomised trials and systematic reviews (with and without metanalyses) comparing women who did and did not receive prepregnancy care. In line with prior work in this area, we will exclude review reports and reports of conference proceedings or abstracts when there is no complete description of the trial or study [81].

6.3.2.4 Type of Intervention

We will use a similar definition of prepregnancy care as Wahabi and colleagues [81]. This includes the following as a sole intervention or in combination for women with type 1 and/or type 2 diabetes:

(i) Glycaemic control by insulin, oral pharmacological agents and/or diet aiming at fasting blood glucose ≤5.7mmol/L and/or postprandial blood glucose ≤7.8mmol/L and/or HbA1c ≤53 mmol/mol (7.0%).

(ii) Counselling and/or education about diabetes complications during pregnancy, the importance of

glycaemic control and self-monitoring of blood glucose level.

(iii) Prepregnancy screening and treatment of complications of diabetes e.g. retinopathy, nephropathy, hypertension.

(iv) The use of contraception until optimization of glycaemic control is achieved.

(v) Vitamin or folic acid supplementation in the prepregnancy period.

6.3.2.5 Participants

Women of reproductive age with pregestational diabetes mellitus who were not pregnant at the time of intervention.

6.3.2.6 Study Assessment

An initial selection of studies identified from the search will be performed using the predetermined review inclusion criteria. Two reviewers (FPD and AME) will independently assess the title and abstracts of selected studies. Full texts of studies meeting the inclusion criteria, or where there is uncertainty regarding inclusion at title and abstract screening, will be retrieved and reviewed with final decisions on inclusion/exclusion achieved through consensus. In case of disagreement, a third independent reviewer (VS) will be consulted.

6.3.2.7 Data Extraction

The following data will be extracted from each study: study design, author details, year and journal of publication, targeted condition, (i.e. type 1 or type 2 diabetes, or both), intervention(s) under investigation, each effectiveness outcome specified in methods and/or findings, whether the outcome was defined or not, the definition used, the indicators and/or tools(s) used to measure the outcome(s) and the time point or period of outcome measurement. Two review authors (AME

and FPD) will extract data independently, review the data together, assess consensus and ensure that all outcomes have been identified. Disagreement will be resolved through discussion. Where a resolution is not possible a third reviewer (VS) will be consulted.

6.3.2.8 Data Analysis and Presentation:

Data will be tabulated so that each study is listed and all outcomes measured in each study displayed separately. Following this, outcomes will be further grouped under domains (eg. maternal outcomes and neonatal outcomes), following a review of the outcomes by AME, FPD and DD. The number of outcomes used to reflect each domain and the number of different definitions and methods of measurements used will be described.

Figure 6.1: Systematic Review Search Strategies

Cochrane Library
1989 – 29/04/2015

#1. "prepregnancy":ti,ab,kw (Word variations have been searched)	75
#2. "pre-pregnancy" :ti,ab,kw (Word variations have been searched)	68
#3. "pre-conception" :ti,ab,kw (Word variations have been searched)	9
#4. "preconception" :ti,ab,kw (Word variations have been searched)	126
#5. #1 or #2 or #3 or #4 270	
#6. "diabetes" :ti,ab,kw (Word variations have been searched)	29,331
#7. #5 and #6 65	

Web of Science
1998 – 29/04/2015

#1. TOPIC: (type 1 diabetes)	86,057
#2. TOPIC: (type 2 diabetes)	116,204
#3. #2 or #1	142,451
#4. TOPIC: (prepregnancy care)	431
#5. TOPIC: (pre-pregnancy care)	308
#6. TOPIC: (pre-conception care)	101
#7. TOPIC: (preconception care)	918
#8. #7 OR #6 OR #5 OR #4	1,593
#9. #8 AND #3	171

EMBASE
1990 – 29/04/2015
('type 1 diabetes'/exp or 'type 1 diabetes' or 'type 2 diabetes'/exp or 'type 2 diabetes') and
(('prepregnancy care'/exp or 'prepregnancy care' or 'preconception care'/exp or 'preconception care') or ('pre conception' and care) or ('pre pregnancy' and care)) and [female]/lim and [humans]/lim
403

CINAHL
1988 – 29/04/2015

S1	type 2 diabetes mellitus OR type 1 diabetes mellitus	51,297
S2	prepregnancy care or preconception care	1,232
S3	pre-pregnancy care or pre-conception care	50
S4	preconception or pre-conception	871
S5	prepregnancy or pre-pregnancy	2,173
S6	S2 OR S3 OR S4 OR S5	2,598
S7	S1 AND S6	141

MEDLINE
1946 – 29/04/2015
1 Diabetes Mellitus, Type 1/ or Diabetes Mellitus, Type 2/ or Diabetes Mellitus/ (228389)
2 pre-pregnancy.mp. (1494)
3 prepregnancy.mp. (1886)
4 Preconception Care/ or pre-conception.mp. (1676)
5 pre-conception.mp. (243)
6 2 or 3 or 4 or 5 (4868)
7 1 and 6 (315)

6.3.3 Part 2: Developing a Consensus on Outcomes Important to Different Stakeholders Using a Delphi Survey and Consensus Meeting

6.3.3.1 Delphi Survey Method

To develop consensus on outcomes of importance to key stakeholders for inclusion in the COS, a Delphi method will be adopted. This method is iterative and uses a series of rounds of data collection and analysis to condense the opinions of individuals into a group consensus. Typically, it involves the use of sequential rounds of questionnaires designed to elicit participants' opinions on a particular topic. Responses to each round are collated, analysed and redistributed to participants for further comment in successive rounds[203]. This technique has advantages over less structured methods of reaching consensus such as round-table discussions. It avoids a situation where certain individuals can dominate a discussion or where other individuals feel obliged to agree with the opinions of more senior members [206]. It also facilitates wide international participation and increased numbers of stakeholders informing the prioritisation process. To improve efficiency, the questionnaire will be completed online using QuestionPro software (http://www.questionpro.com) or similar such software appropriate to online survey design.

The list of potential outcomes finalised from part 1 will be formatted into a list of outcomes with a response designed to allow the participants rate each one of the outcomes on a 9 point Likert type scale with higher values representing increased importance for inclusion of the outcome in the COS. Following review of the outcome list by the research group (AME, VS, DD & FPD), the list will be circulated to the study advisory group (SAG). The SAG, composed of key stakeholders, will be asked to comment on the overall list of outcomes and the suitability of the domain under which they

are grouped. They will be additionally asked to list any additional outcomes that they think should be included. These additional outcomes will be added to the list of outcomes for inclusion in the Delphi survey. Members of the SAG will not participate in the Delphi exercise as they had a role in study design and this may influence scoring. Instead, they will be invited to participate in the final consensus meeting.

6.3.3.2 Delphi Survey Participants

The key stakeholders include women, clinicians and researchers. Women, who represent service users, will have a known diagnosis of type 1 or type 2 diabetes mellitus or represent women with such diagnoses Recruitment will include listed groups of diabetes services users (eg. Diabetes Ireland) accessed via the electronic discussion e-mail list manager. The manager will be emailed with information on the survey and a request to distribute an invitation email to members on their email lists. The list managers will have an opportunity to contact the researcher directly to clarify any issues or to seek further information about the survey and the research prior to making a decision. The distribution of the survey will be at the discretion of the email list manager. Clinical leads at participating hospitals will also be asked to invite service users to participate via their prepregnancy and diabetes care clinical teams. Clinicians will include obstetricians, endocrinologists, midwives, diabetes midwife/nurse specialists and dieticians. Researchers with expertise in diabetes care will be also invited to participate. Clinicians and researchers will be invited from specialist centres globally. Clinical leads will be identified and recruited through the DPSG (Diabetes in Pregnancy Study Group) - a study group of the EASD (European Association for the Study of Diabetes). These clinical leads will be invited to participate by email and will be asked to forward the study details to other members of their prepregnancy care team.

Snowball sampling will be used, whereby participants from all the above groups will be asked to forward the invitation to others whom they regard as having the required expertise. Although there is no consensus on the ideal number of participants for a Delphi, we will aim for a total of 180 participants – including at least 30 service users [203,207]. Each participant will be emailed a letter of invitation outlining the study and the link to the online survey. Informed consent to participate in the study will be obtained from each participant when they register for the online Delphi questionnaire. The consent process will occur prior to submission of any answers. The importance of completing the whole Delphi Process will be emphasised and generic reminder emails will be sent to aid completion of each round. A unique identifier will be assigned to each participant, tracked to his or her email address, and this will allow monitoring of attrition at each round.

6.3.3.3 Delphi Survey Round 1

The online questionnaire will request the participant's name, email address and centre for which they are aligned in either receiving (users) or providing/researching on prepregnancy diabetes care (clinicians/researchers). Participants will be asked to identify the stakeholder group and subgroup to which they belong. They will be asked to complete the questionnaire within three weeks and will be prompted after week two with an email reminder. The questionnaires will contain lay terminology alongside clinical terms to assist women in understanding complex terminology.

The list of outcomes to be scored will be ordered alphabetically to avoid weighting of outcomes caused by the ordering in which they are displayed. There will be an option for a participant to add up to two additional outcomes and provide an associated score. They will be asked the key question: 'Prepregnancy care for women with pre-existing

diabetes can have a variety of beneficial effects, each of which could be measured as an outcome in a clinical study. Please score how important each of the following outcomes are on a scale of 1-9.' Scores will be grouped into 1 to 3 = not important; 4 to 6 = important but not critical; or 7 to 9 = critical. This scale was devised by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) and has been adopted in other core outcome development research groups using the Delphi method[195,207].

6.3.3.4 Analysis of Delphi Survey Round 1

The results of round 1 will be summarised using descriptive statistics including the proportion of participants scoring for each rating point on the Likert scale (i.e., for each point 1 to 9). Any additional outcomes listed will be reviewed by the researchers (AME and FPD). If they are deemed to represent a new outcome based on this review, they will be included for round two and the SAG will be consulted to review if appropriate. All outcomes will be carried forward to round two. Of note, continuation to round 2 will be considered based on the response to round one. If a low number of responders (<10) are observed for one or more stakeholder groups, the Delphi protocol for future rounds will be reviewed and revised. Where there is only one stakeholder group with a small number of respondents, then consideration will be given to grouping with another stakeholder group following consultation with the SAG to ensure appropriateness of grouping.

6.3.3.5 Delphi Survey Round 2

Participants, who respond to round 1, will be forwarded the round 2 questionnaire and asked to complete online. Each participant will be presented with the number of respondents and distribution of score for each outcome as per stakeholder

group. They will also be shown their score from round 1, asked to consider responses from the other members of the stakeholder groups and invited to rescore the outcome.

6.3.3.6 Analysis of Delphi Survey Round 2

The results of round 2 will be summarised using descriptive statistics. The number of participants taking part will be recorded. For each outcome, the number of participants who have scored the outcome and the distribution of scores will be noted. All outcomes that have a median score of ≥4 for any group will be carried forward to round 3. Participants who completed round 1 and 2 will be invited to complete round 3.

6.3.3.7 Delphi Survey Round 3

Participants, who respond to round 1 and 2, will be forwarded the round 3 questionnaire and asked to complete online. Again, each participant will be presented with the number of respondents and distribution of score for each outcome for their particular stakeholder group. They will also be shown their score from round 2, asked to consider responses from other members of the stakeholder group and asked to rescore the outcome.

6.3.3.8 Analysis of Delphi Survey Round 3

The results of round 3 will be summarised using descriptive statistics. The number of participants taking part will be recorded. For each outcome, the number of participants who have scored the outcome and the distribution of scores will be noted. Each outcome will be classified as 'consensus in', 'consensus out' or 'no consensus' according to the classifications in table 1. Although these cut-offs are subjective, they have previously been described in a COS protocol and are pre-specified to reduce researcher bias[195]. The

results of this process will be brought forward to the consensus group meeting.

6.3.3.9 Consensus Group Meeting Method

This final phase will be a face-to-face meeting with key stakeholders. The meeting participants will be sampled purposively to ensure a range of views of patients, clinicians and researchers with expertise in diabetes care. The sample will be drawn from those who completed all rounds of the Delphi study. The results from each round of the Delphi survey will be presented. Review of the responses from round three of the Delphi exercise will inform the structure and content of the meeting. The objective of the consensus meeting is to discuss outcomes about which there was disagreement in round three of the Delphi study, and to validate and agree on a list of final outcomes which will constitute the COS.

6.3.3.10 Consensus Group Meeting Participants

The consensus group will include, at a minimum, two representatives from obstetrics, endocrinology, midwifery, diabetes specialist nursing, dietetics; at least three service users; and members of the SAG. A half-day meeting is planned and to achieve effective consensus the facilitator will ensure that the meeting is collaborative, cooperative, egalitarian, inclusive and participatory.

6.4 Conclusions

There is currently no COS for studies assessing the effectiveness of prepregnancy care for women with pregestational diabetes mellitus. The development of such a COS in this clinical area aims to improve the interpretation and comparison of future studies while reducing the risk of outcome reporting bias. We will involve key stakeholders and

use recognised techniques to ensure that the ensuing COS is suitable and well accepted in future research.

Chapter 7: A Core Outcome Set for Studies Evaluating the Effectiveness of Prepregnancy Care for Women with Pregestational Diabetes

Egan AM, Galjaard S, Maresh M, Loeken MR, Napoli A, Anastasiou E, Noctor E, De Valk H, Van Poppel M, Todd M, Smith V, Devane D, Dunne FP.
A Core outcome set for studies evaluating the effectiveness of prepregnancy care for women with pregestational diabetes.
In Press Diabetologia March 2017.

7.1 Introduction

Women with pregestational diabetes (including type 1 and type 2) have an increased risk of adverse pregnancy outcomes including congenital anomalies, stillbirth and perinatal mortality [57,58]. It is well established that this risk can be reduced by attendance at prepregnancy care[67,101]. Prepregnancy care describes the targeted support and additional care offered to women who are planning pregnancy [67]. It typically involves regular review by a multidisciplinary diabetes team in a dedicated outpatient clinic. In general, woman attending prepregnancy care undergo a full medication review, assessment and treatment of diabetes complications as required and optimisation of glycaemic control. However, there is not an agreed proforma for delivery of this care and while many groups have reported positive benefits associated with specific programmes, the outcomes reported are varied[67,73,101]. This inconsistency raises concern for outcome selection bias, makes meaningful comparison between studies difficult, and limits the ability to combine individual studies' findings into summary estimates[208]. One approach to overcome this lack of uniformity is to develop a COS or an agreed set of outcomes. The goal is that the COS will be collected and reported in all studies that report a specific clinical condition[196]. It represents a minimum that should be collected and reported, but does not restrict researchers from adding additional outcomes at their discretion. The development of COS across multiple disciplines is supported by the COMET initiative, which brings together interested researchers and minimises duplication of work[196,201]. The Core Outcome Set – Standards for reporting (COS-STAR) statement aims to standardise COS reporting for the benefit of all users (appendix 4)[209]. More specifically, in the field of women's health, the editors of over 50 journals recently endorsed the CROWN Initiative[202]. Launched in 2014, this initiative has a number of aims which include encouraging COS development and facilitating effective dissemination of manuscripts.

7.2 Study Objective

In this paper we present a study on the development of a COS for trials and other studies evaluating the effectiveness of prepregnancy care for women with pregestational diabetes mellitus.

7.3 Methods

7.3.1 Registration

This study is registered in the COMET database and a detailed study protocol was published previously[208,210].

7.3.2 Ethics

Ethical approval for the study was obtained from the Galway University Hospitals' ethics committee.

7.3.3 Summary

The COS was developed by completing a systematic literature review to identify all outcomes reported in prior studies in this area. Key stakeholders then prioritised these outcomes using a Delphi study, providing a preliminary COS. The list of outcomes included in the final COS were finalised at a face-to-face consensus meeting.

7.3.4 Systematic Review

The search strategy took place according to the previously described protocol[208]. We included prospective cohort studies, case-control studies, randomised trials and systematic reviews published in the English language that evaluated prepregnancy care for women with diabetes. Two reviewers (FPD and AME) independently assessed the titles and abstracts of identified studies. Full texts of studies meeting the inclusion criteria (or in the case of uncertainty regarding inclusion) were retrieved and consensus was achieved on inclusion status. The reviewers then extracted the following data from each study: study design, author details, year and

journal of publication, targeted condition, intervention under investigation, each outcome specified in methods or findings, definition and method of collection used (if available) and time points or periods of outcome measurement. Following review by FPD, AME, DD and three additional key stakeholders forming the SAG, outcomes were grouped under three domains: measures of pregnancy preparation, maternal outcomes and neonatal outcomes.

7.3.5 Delphi Study

Questionnaires were completed online using SurveyMethods software (www.surveymethods.com). Participants were recruited from people within the following groups: women with diabetes, midwives, obstetricians, paediatricians/neonatologists, policy-makers, other service providers and researchers with an interest in diabetes in pregnancy. We sent an email inviting participation to the list managers in the following organisations: DPSG, IADPSG, Diabetes Ireland (DI), Irish Endocrine Society (IES), FIGO, European Board and College of Obstetrics and Gynaecology (EBCOG), EASD, Irish Nutrition and Dietetic Institute (INDI), Irish Institute of Obstetricians and Gynaecologists and Saolta Healthcare Group (Ireland). Snowball sampling was encouraged (ie. participants were asked to forward the invitation to others whom they regarded as having the required expertise).

In the round 1 survey instrument, outcomes identified following the systematic review were presented to participants, grouped by domain. Related outcomes were presented alongside each other (eg. measures of glucose control during pregnancy). Participants were asked to rate each one on a 9-point Likert-type scale with higher values representing increased importance for inclusion in the COS. Participants had an opportunity to list additional outcomes for consideration in subsequent rounds of the COS. Consent was obtained prior to the submission of any answers and the following information was also requested: name, email address, gender, stakeholder group and country of residence. The results of round 1 were summarised using descriptive statistics. All outcomes were

carried forward to round 2 including additional outcomes suggested by participants in round 1. Participants who responded to round 1 were invited to participate in round 2. In round 2, they were shown their score from round 1 and presented with the distribution of scores for each outcome per stakeholder group. Participants were invited to re-score the outcome. All outcomes that had a median score of ≥4 for any group were carried forward to round 3. Participants who completed round 1 and 2 were invited to complete round 3. Each participant was presented with their round 2 scores and the distribution of scores for each outcome as per stakeholder group. Participants were asked to re-score the outcome. Outcomes were classified as 'consensus in' (≥70% participants scoring as 7-9 and <15% scoring as 1-3), 'consensus out' (≥70% scoring as 1-3 and <15% scoring as 7-9) or 'no consensus' (anything else) [195].

7.3.6 Consensus Meeting

This final phase involved a face-to-face meeting with key stakeholders representing a range of views of patients, clinicians and researchers. The meeting was chaired by DD who did not vote at the meeting. Outcomes classified as 'consensus in' or 'no consensus' were presented to the group along with the response results from round 3 of the Delphi study. There was opportunity for open discussion and for combining or modifying individual outcomes. Participants were asked to vote on each listed outcome as 'yes' or 'no' for inclusion or exclusion in the final COS. Outcomes for which ≥70% participants voted 'yes' were carried forward to a further discussion and a 2nd, final, vote. The outcome was included in the COS when ≥70% participants voted 'yes' in this final vote. Participants used Poll Everywhere, a downloadable application to place their vote anonymously (www.polleverywhere.com).

7.4 Results

7.4.1 Systematic review

A total of 1127 titles and abstracts were identified. Following review of the title and/or abstracts, 90 full text papers were retrieved and assessed for eligibility. A further 57 papers were excluded following full text review based on the criteria mentioned in the methods section leaving 33 papers in the review[67,73,101,104-110,112,113,211-231] (figure 7.1). Following data extraction, 86 individual outcomes were identified. These were grouped according to the following domains: measures of pregnancy preparation (n=38), neonatal outcomes (n=32) and maternal outcomes (n=16).

7.4.2 Delphi Study

The 86 outcomes extracted were presented to the participants grouped by domain. There were 151 respondents to the round 1 instrument (74.2% female) with representation from 24 countries and 5 continents. A total of 72.2% respondents were from Ireland and the United Kingdom. Stakeholders were grouped into 3 categories. Category 1 consisted of endocrinologists (n=43, 28.5%), diabetes nurse specialists (n=8, 5.3%) and dieticians (n=2, 1.3%). Category 2 consisted of midwives (n=17, 11.3%) and obstetricians (n=23, 15.2%). Category 3 consisted of women with diabetes (n=20, 13.2%), policy makers (n=1, 0.7%), researchers in the area of diabetes (n=14, 9.3%), advocates on behalf of those with diabetes (n=2, 1.3%) and others (n=21, 13.9%). Those that selected 'other' were from a variety of healthcare backgrounds and included general practitioners, anaesthesiologists and neonatologists. Table 7.1 outlines the median score for each outcome based on the response to the round 1 instrument. An additional 27 outcomes were suggested by round 1 respondents and included in round 2.

Round 2 participants were asked to rate 113 outcomes as follows: measures of pregnancy preparation (n=51), neonatal outcomes (n=39) and maternal outcomes (n=23). The round 2 instrument was completed by 120 people who had completed round 1 (78.4%). Table 7.1 outlines the median score for each outcome based on the responses to the round 2 instrument. All outcomes had a median score of ≥4 and therefore 113 outcomes were carried forward to round 3.

The round 3 instrument was completed by 101 participants who had completed round 2 (84.2%) and the median score for each outcome is outlined in table 7.1. Table 7.2 outlines the percentage of round 3 participants scoring each outcome as 1-3, 4-6 and 7-9 on the 9-point scale. A total of 84 (74.3%) outcomes were classified as 'consensus in' and 29 (25.7%) were classified as 'no consensus'.

7.4.3 Consensus Meeting

The consensus meeting involved 14 stakeholders, a chairperson and 2 administrators. The stakeholders included 2 women with type 1 diabetes, 5 endocrinologists, 1 diabetes nurse specialist, 2 midwives, 2 obstetricians and 2 researchers in the area of diabetes and pregnancy. Table 7.3 outlines the percentage of participants voting yes for each outcome in rounds 1 and 2. Based on the views of the group, a number of outcomes were rephrased and/or combined. These are as follows: 'physician review prior to conception' was rephrased to 'healthcare professional review prior to conception'; 'maternal weight at initial antenatal visit' was combined with 'body mass index at 1st antenatal visit'; 'maternal weight at birth of baby' was combined with 'gestational weight gain'; 'systolic blood pressure at 1st antenatal visit' and 'diastolic blood pressure at initial antenatal visit' were combined to form the new outcome of 'blood pressure at 1st antenatal visit'; 'HbA1c when first attending prepregnancy care' and 'HbA1c at referral to prepregnancy care' and 'preconception HbA1c' were combined to form 'HbA1c at 1st attendance at prepregancy care'.

Voting took place on each outcome in the modified list of outcomes (n=108). Following round 1 voting, 20 outcomes were considered for inclusion in the COS. However following discussion and round 2 voting, 17 outcomes were selected and agreed on for inclusion in the final COS as outlined in table 7.4. In the domain of measures of pregnancy preparation the following outcomes (n=9) were included: 'healthcare professional review prior to conception', 'smoking status at 1st antenatal visit', 'use of folic acid preconception', 'thyroid function at 1st antenatal visit', 'use of

potentially teratogenic medications at conception', 'gestational age at 1st antenatal visit', 'body mass index at 1st antenatal visit', 'blood pressure at 1st antenatal visit', '1st trimester HbA1c'. In the domain of neonatal outcomes the following outcomes (n=6) were included: 'perinatal mortality', 'miscarriage', 'congenital malformation', 'preterm birth', 'large for gestational age' and 'small for gestational age'. In the domain of maternal outcomes, the following outcomes (n=2) were included: 'gestational weight gain' and 'severe maternal hypoglycaemia in 1st trimester'.

Figure 1: Selection of Studies for Systematic Review

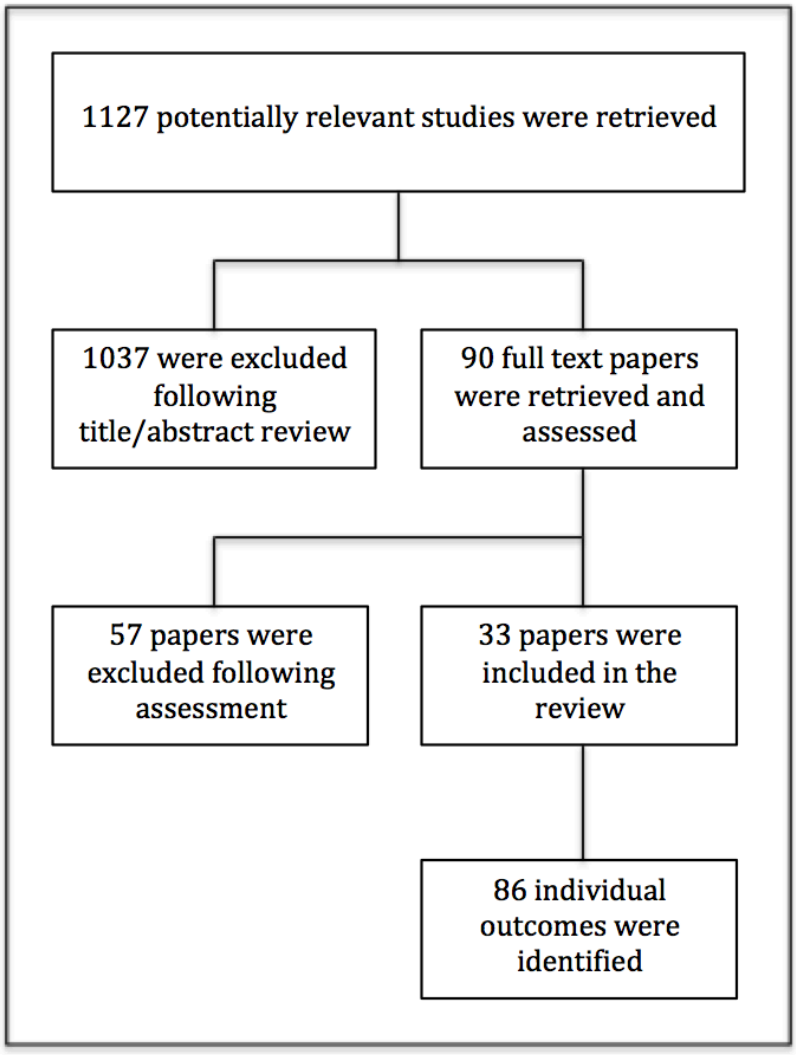


Table 7.1: Outcomes Included in Delphi Study and Median Score for Each Outcome

	Round 2 (120 respondents) Median Scores	Round 3 (101 Respondents) Median Scores
Measures of Pregnancy Preparation		
Patient attendance at prepregnancy care	9	9
Physician review prior to conception	9	8
Discontinuation of contraception for purposes of pregnancy	8	9
Self-reported planned pregnancy at initial antenatal visit	8	7
Attendance rate at prepregnancy care appointments [a]	8	8
Physician assessment of level of pregnancy preparation.[a]	8	7
Asssessment of maternal health-related quality of life[*]	8	7
Duration of prepregnancy care [a]	7	7
Patient satisfaction with prepregnancy care [a]	8	7
Smoking status during pregnancy	9	9
Smoking status at 1st antenatal visit	9	9
Use of folic acid preconception	9	9
Use of folic acid at 1st antenatal visit	9	9
Thyroid function at 1st antenatal visit [a]	8	8
Rubella status at 1st antenatal visit [a]	9	9
Iron Status at 1st antenatal visit [a]	7	7
Vitamin B12 level at 1st antenatal visit [a]	7	7
Vitamin D level at initial antenatal visit	7	7
Use of potentially teratogenic meds at conception	9	9
Alcohol intake during pregnancy	9	9
Gestational age at 1st antenatal visit	9	9
Maternal weight at initial antenatal visit	9	9
Maternal weight at birth of baby	8	8
Body mass index at initial antenatal visit	9	9
Systolic blood pressure at initial antenatal visit	9	9
Diastolic blood pressure at initial antenatal visit	9	9
HbA1c when first attending prepregnancy care	9	9
HbA1c at referral to prepregnancy care	9	8
Preconception HbA1c	9	9
HbA1c during pregnancy	9	9
1st trimester HbA1c	9	9
2nd trimester HbA1c	9	9
3rd trimester HbA1c	9	9
HbA1c at birth of baby	8	8
HbA1c postpartum	7	7
HbA1c at 9 weeks	8	7
HbA1c at 12 weeks	8	8
HbA1c at 14 weeks	8	7
HbA1c at 16 weeks	7.5	7
HbA1c at 20 weeks	8	7
HbA1c at 24 weeks	8	7
HbA1c at 26 weeks	8	7
HbA1c at 28 weeks	8	7
HbA1c at 32 weeks	8	7
HbA1c at 36 weeks	8	7
Per-trimester fasting and pre-prandial glucose	9	9
Per-trimester 90 minute post-prandial glucose	8	7
Per-trimester 60 minute post-prandial glucose [a]	8	8
Fructosamine level during pregnancy [a]	7	6
Patient compliance with glucose monitoring [a]	9	9

Patient compliance with medication/insulin regimen [a]	9	9
Neonatal Outcomes		
Shoulder dystocia	9	9
Clavicular fracture	9	9
Erb's palsy	9	9
Infant respiratory distress syndrome	9	9
Need for mechanical ventilation [a]	9	9
Neonatal hyperbilirubinemia	8	8
Neonatal hyperbilirubinemia requiring treatment [a]	8.5	8
Neonatal hypocalcaemia	8	8
Apgar score at 1 minute	9	9
Apgar score at 5 minutes	9	9
Cord Ph at birth [a]	8	8
Birth Asphyxia [a]	9	9
Neonatal encephalopathy [a]	9	9
Method of feeding infant [a]	9	9
Livebirth	9	9
Stillbirth	9	9
Neonatal death	9	9
Perinatal mortality	9	9
Miscarriage	9	9
Termination of pregnancy	9	9
Termination for foetal malformation	9	9
Termination for non-diabetes associated issue	8	7
Congenital malformation	9	9
Major congenital malformation	9	9
Weeks of gestation at delivery	9	9
Preterm birth	9	9
Extremely preterm birth	9	9
Infant birth weight at delivery	9	9
Large for gestational age	9	9
Macrosomia	9	9
Small for gestational age	9	9
Low birth weight	9	9
Composite adverse outcome	8	9
Admission to neonatal intensive care unit	9	9
Admission to routine postnatal ward	7	7
Length of stay in neonatal intensive care unit	9	9
Neonatal hypoglycaemia	9	9
Severe neonatal hypoglycaemia	9	9
Neonatal hypoglycaemia requiring intravenous treatment [a]	9	9
Maternal Outcomes		
Gestational hypertension	9	9
Pre-eclampsia	9	9
Mode of birth	9	9
Normal vaginal birth	9	9
Instrumental birth	9	8
Caesarean birth	9	9
Planned / elective lower segment caesarean section	9	8
Emergency lower segment caesarean section	9	9
Trial of labour	8	8
Gestational weight gain	9	9
Presence of nephropathy	9	9
Nephropathy progression	9	9

Presence of retinopathy	9	9
Retinopathy Progression	9	9
Presence of peripheral neuropathy [a]	9	9
Peripheral neuropathy progression [a]	9	9
Presence of autonomic neuropathy [a]	9	9
Severe maternal hypoglycaemia	9	9
Maternal mortality	9	9
Symphysis pubis dysfunction [a]	7	7
Maternal post partum infection [a]	8	8
Maternal inpatient admission during pregnancy [a]	8	8
Maternal length of stay in hospital during pregnancy and delivery [a]	8	8

[a] outcomes added to round 2 and 3 instruments.

Table 7.2: Percentage of Round 3 Participants (n=101) Scoring Each Outcome as 1-3, 4-6 or 7-9 on the 9 Point Scale [a]

	Score 1-3	Score 4-6	Score 7-9
Measures of Pregnancy Preparation			
Patient attendance at prepregnancy care	0 %	3 %	97.0%
Physician review prior to conception	11.9%	6.9%	77.2%
Discontinuation of contraception for purposes of pregnancy[b]	11.8%	16.8%	69.3%
Self-reported planned pregnancy at initial antenatal visit[b]	12.9%	15.8%	68.3%
Attendance rate at prepregnancy care appointments	4.9%	11.8%	81.1%
Physician assessment of level of pregnancy preparation[b]	10.9%	19.8%	66.3%
Asssessment of maternal health-related quality of life[b]	10.9%	27.7%	59.4%
Duration of prepregnancy care[b]	7.9%	26.7%	63.4%
Patient satisfaction with prepregnancy care[b]	7.9%	21.7%	66.3%
Smoking status during pregnancy	8.9%	0.9%	89.1%
Smoking status at 1st antenatal visit	3%	13.9%	91.1%
Use of folic acid preconception	0%	1%	99.0%
Use of folic acid at 1st antenatal visit	8.9%	3%	87.1%
Thyroid function at 1st antenatal visit[b]	8.9%	14.9%	66.3%
Rubella status at 1st antenatal visit	10.9%	14.9%	73.3%
Iron Status at 1st antenatal visit[b]	110.9%	27.7%	59.4%
Vitamin B12 level at 1st antenatal visit[b]	12.9%	25.7%	59.4%
Vitamin D level at initial antenatal visit[b]	12.9%	31.7%	55.4%
Use of potentially teratogenic meds at conception	0.9%	0%	98.0%
Alcohol intake during pregnancy	1.9%	4%	92.1%
Gestational age at 1st antenatal visit	0.9%	0.9%	98.0%
Maternal weight at initial antenatal visit	8.9%	5.9%	84.9%
Maternal weight at birth of baby	7.9%	12.9%	78.2%
Body mass index at initial antenatal visit	0%	6.9%	91.1%
Systolic blood pressure at initial antenatal visit	0.9%	5.9%	91.1%
Diastolic blood pressure at initial antenatal visit	0.9%	6.9%	90.1%
HbA1c when first attending prepregnancy care	6.9%	3%	89.1%
HbA1c at referral to prepregnancy care	10.9%	12.9%	72.3%
Preconception HbA1c	4%	4%	90.1%
HbA1c during pregnancy	4%	4%	90.1%
1st trimester HbA1c	7.9%	2%	87.1%
2nd trimester HbA1c	8.9%	8.9%	80.1%
3rd trimester HbA1c	8.9%	6.9%	81.2%
HbA1c at birth of baby[b]	12.9%	20.8%	65.3%
HbA1c postpartum[b]	14.9%	21.8%	60.4%
HbA1c at 9 weeks[b]	15.8%	22.8%	61.4%
HbA1c at 12 weeks[b]	13.9%	19.8%	63.4%
HbA1c at 14 weeks[b]	16.8%	2%	81.2%
HbA1c at 16 weeks[b]	16.8%	27.7%	55.5%
HbA1c at 20 weeks[b]	15.8%	26.7%	57.5%
HbA1c at 24 weeks[b]	14.9%	24.9%	60.2%
HbA1c at 26 weeks[b]	16.8%	28.7%	54.5%
HbA1c at 28 weeks[b]	15.8%	25.7%	58.5%
HbA1c at 32 weeks[b]	16.8%	24.9%	58.3%
HbA1c at 36 weeks[b]	15.8%	21.8%	62.4%
Per-trimester fasting and pre-prandial glucose	10.9%	4.9%	82.2%
Per-trimester 90 minute post-prandial glucose[b]	13.9%	16.8%	69.3%
Per-trimester 60 minute post-prandial glucose	10.9%	10.9%	78.2%
Fructosamine level during pregnancy[b]	17.8%	34.7%	47.5%
Patient compliance with glucose monitoring	10.9%	6.9%	79.2%
Patient compliance with medication/insulin regimen	10.9%	4.9%	82.2%

Neonatal Outcomes			
Shoulder dystocia	0%	4%	94.9%
Clavicular fracture	4.9%	9.9%	81.2%
Erb's palsy	4%	5.9%	87.1%
Infant respiratory distress syndrome	3%	3%	91.1%
Need for mechanical ventilation	4.9%	6.9%	85.1%
Neonatal hyperbilirubinemia	3%	15.8%	77.2%
Neonatal hyperbilirubinemia requiring treatment	5.9%	10.9%	81.2%
Neonatal hypocalcaemia	4.9%	15.8%	76.2%
Apgar score at 1 minute	4%	8.9%	84.9%
Apgar score at 5 minutes	1%	3%	94.9%
Cord Ph at birth	6.9%	15.8%	73.3%
Birth Asphyxia	8.9%	4%	83.2%
Neonatal encephalopathy	8.9%	8.9%	79.2%
Method of feeding infant	2%	12.9%	81.2%
Livebirth	2%	0%	94.1%
Stillbirth	2%	1%	95%
Neonatal death	2%	2%	94.9%
Perinatal mortality	6.9%	2%	89.1%
Miscarriage	2%	5.9%	89.1%
Termination of pregnancy	6.9%	15.8%	75.2%
Termination for foetal malformation	8.9%	3%	86.1%
Termination for non-diabetes associated issue	13.9%	15.8%	67.3%
Congenital malformation	1%	2%	93.1%
Major congenital malformation	6.9%	2%	85.1%
Weeks of gestation at delivery	1%	0%	96%
Preterm birth	6.9%	4.9%	86.1%
Extremely preterm birth	8.9%	6.9%	80.2%
Infant birth weight at delivery	0%	3%	94.9%
Large for gestational age	3%	5.9%	88.1%
Macrosomia	7.9%	9.9%	79.2%
Small for gestational age	4%	3%	87.1%
Low birth weight	9.9%	8.9%	77.2%
Composite adverse outcome	7.9%	9.9%	75.2%
Admission to neonatal intensive care unit	0%	2%	96%
Admission to routine postnatal ward	9.9%	15.8%	46.5%
Length of stay in neonatal intensive care unit[b]	4.9%	10.9%	80.1%
Neonatal hypoglycaemia	0.9%	2%	94.9%
Severe neonatal hypoglycaemia	9.9%	7.9%	82.2%
Neonatal hypoglycaemia requiring intravenous treatment	7.9%	12.9%	85.1%
Maternal Outcomes			
Gestational hypertension	2%	2%	95%
Pre-eclampsia	2%	2%	95%
Mode of birth	2%	7.9%	87.1%
Normal vaginal birth	8.9%	12.9%	74.9%
Instrumental birth	8.9%	10.9%	77.2%
Caesarean birth	8.9%	9.9%	78.2%
Planned / elective lower segment caesarean section	9.9%	10.9%	75.2%
Emergency lower segment caesarean section	9.9%	5.9%	80.2%
Trial of labour[b]	9.9%	15.8%	69.3%
Gestational weight gain	0.9%	6.9%	86.1%
Presence of nephropathy	8.9%	4.9%	84.9%
Nephropathy progression	0.9%	2%	94.9%

Presence of retinopathy	8.9%	4%	83.2%
Retinopathy Progression	0.9%	3%	94.9%
Presence of peripheral neuropathy	9.9%	7.9%	78.2%
Peripheral neuropathy progression	4%	6.9%	85.1%
Presence of autonomic neuropathy	9.9%	6.9%	79.2%
Severe maternal hypoglycaemia	0%	2%	96%
Maternal mortality	0%	0.9%	96%
Symphysis pubis dysfunction[b]	9.9%	29.7%	60.4%
Maternal post partum infection[b]	10.9%	18.8%	67.3%
Maternal inpatient admission during pregnancy	6.9%	15.8%	74.9%
Maternal length of stay in hospital during pregnancy and delivery[b]	9.9%	17.8%	69.3%

[a] Instances of cumulative scores not reaching 100% result from participants leaving an outcome undefined.

[b] Indicates that the outcome was classified as "no consensus". Remaining outcomes were classified as "consensus in".

Table 7.3: % Consensus Meeting Participants Voting "yes" to Include Each Outcome in the Final Core Outcome Set

	Round 1 Voting (% voting yes)	Round 2 Voting (% voting yes)
Measures of Pregnancy Preparation		
Patient attendance at prepregnancy care	78.6%	0%
Healthcare professional review prior to conception[a]	71.4%	100%
Discontinuation of contraception for purposes of pregnancy	7.1%	-
Self-reported planned pregnancy at initial antenatal visit	14.3%	-
Attendance rate at prepregnancy care appointments	7.1%	-
Physician assessment of level of pregnancy preparation	0%	-
Asssessment of maternal health-related quality of life	14.3%	-
Duration of prepregnancy care	7.1%	-
Patient satisfaction with prepregnancy care	14.3%	-
Smoking status during pregnancy	42.9%	-
Smoking status at 1st antenatal visit[a]	85.7%	100%
Use of folic acid preconception[a]	100%	100%
Use of folic acid at 1st antenatal visit	35.7%	-
Thyroid function at 1st antenatal visit[a]	71.4%	70%
Rubella status at 1st antenatal visit	57.1%	-
Iron Status at 1st antenatal visit	14.3%	-
Vitamin B12 level at 1st antenatal visit	7.1%	-
Vitamin D level at initial antenatal visit	28.6%	-
Use of potentially teratogenic medications at conception[a]	92.9%	100%
Alcohol intake during pregnancy	35.7%	-
Gestational age at 1st antenatal visit[a]	85.7%	100%
Body mass index at 1st antenatal visit[a]	100%	100%
Blood pressure at 1st antenatal visit[a]	92.9%	100%
HbA1c at first attendance at prepregnancy care	92.9%	60%
HbA1c during pregnancy	7.1%	-
1st trimester HbA1c[a]	100%	100%
2nd trimester HbA1c	21.4%	-
3rd trimester HbA1c	14.3%	-
HbA1c at birth of baby	14.3%	-
HbA1c postpartum	14.3%	-
HbA1c at 9 weeks	0%	-
HbA1c at 12 weeks	0%	-
HbA1c at 14 weeks	0%	-
HbA1c at 16 weeks	0%	-
HbA1c at 20 weeks	0%	-
HbA1c at 24 weeks	0%	-
HbA1c at 26 weeks	0%	-
HbA1c at 28 weeks	0%	-
HbA1c at 32 weeks	0%	-
HbA1c at 36 weeks	0%	-
Per-trimester fasting and pre-prandial glucose	14.30%	-
Per-trimester 90 minute post-prandial glucose	0%	-
Per-trimester 60 minute post-prandial glucose	0%	-
Fructosamine level during pregnancy	0%	-
Patient compliance with glucose monitoring	35.7%	-
Patient compliance with medication/insulin regimen	42.9%	-
Neonatal Outcomes		
Shoulder dystocia	35.7%	-
Clavicular fracture	7.1%	-

Erb's palsy	7.1%	-
Infant respiratory distress syndrome	21.4%	-
Need for mechanical ventilation	7.1%	-
Neonatal hyperbilirubinemia	0%	-
Neonatal hyperbilirubinemia requiring treatment	7.1%	-
Neonatal hypocalcaemia	0%	-
Apgar score at 1 minute	14.3%	-
Apgar score at 5 minutes	28.6%	-
Cord Ph at birth	7.1%	-
Birth Asphyxia	14.3%	-
Neonatal encephalopathy	7.1%	-
Method of feeding infant	42.9%	-
Livebirth	64.3%	-
Stillbirth	50%	-
Neonatal death	42.9%	-
Perinatal mortality[a]	92.9%	100%
Miscarriage[a]	85.7%	100%
Termination of pregnancy	57.1%	-
Termination for foetal malformation	50%	-
Termination for non-diabetes associated issue	7.1%	-
Congenital malformation[a]	85.7%	100%
Major congenital malformation	57.1%	
Weeks of gestation at delivery	41.7%	-
Preterm birth[a]	75%	90%
Extremely preterm birth	75%	0%
Infant birthweight at delivery	41.7%	-
Large for gestational age[a]	75%	90%
Macrosomia	25%	-
Small for gestational age[a]	75%	80%
Low birthweight	0%	-
Composite adverse outcome	8.4%	-
Admission to neonatal intensive care unit	66.7%	-
Admission to routine postnatal ward	8.4%	-
Length of stay in neonatal intensive care unit	58.3%	-
Neonatal hypoglycaemia	41.7%	-
Severe neonatal hypoglycaemia	41.7%	-
Neonatal hypoglycaemia requiring intravenous treatment	25%	-
Maternal Outcomes		
Gestational hypertension	41.7%	-
Pre-eclampsia	50%	-
Mode of birth	8.4%	-
Normal vaginal birth	25%	-
Instrumental birth	0%	-
Caesarean birth	50%	-
Planned / elective lower segment caesarean section	25%	-
Emergency lower segment caesarean section	41.7%	-
Trial of labour	0%	-
Gestational weight gain[a]	83.3%	100%
Presence of nephropathy	8.4%	-
Nephropathy progression	25%	-
Presence of retinopathy	8.4%	-
Retinopathy Progression	25%	-
Presence of peripheral neuropathy	0%	-
Peripheral neuropathy progression	0%	-
Presence of autonomic neuropathy	0%	-

Severe maternal hypoglycaemia in 1st trimester[a]	100%	100%
Maternal mortality	66.7%	-
Symphysis pubis dysfunction	0%	-
Maternal post partum infection	0%	-
Maternal inpatient admission during pregnancy	25%	-
Maternal length of stay in hospital during pregnancy and delivery	8.4%	-

*outcome included in final core outcome set.

Table 7.4: Final Core Outcome Set (COS) to be Included in All Studies of Prepregnancy Care for Women with Pregestational Diabetes (n=17)

Domain	Outcome
Measures of Pregnancy Preparation (n=9)	Healthcare professional review prior to conception Smoking status time at 1st antenatal visit Use of folic acid preconception Thyroid function at 1st antenatal visit Use of potentially teratogenic medications at conception Gestational age at 1st antenatal visit Body mass index at 1st antenatal visit Blood pressure at 1st antenatal visit 1st trimester HbA1c
Neonatal Outcomes (n=6)	Perinatal mortality Miscarriage Congenital malformation Preterm birth Large for gestational age Small for gestational age
Maternal Outcomes (n=2)	Gestational weight gain Severe maternal hypoglycaemia in 1st trimester

7.5 Discussion

7.5.1 Summary and Discussion of Findings

This study identified and agreed 17 core outcomes essential for studies evaluating prepregnancy care for women with pregestational diabetes. These outcomes are grouped according to three domains that include measures of pregnancy preparation, neonatal outcomes and maternal outcomes. It is advocated that all trials and other non-randomized studies and audit in this area use this COS with the aim of improving transparency and the ability to compare and combine future studies with greater ease.

The rationale for the development of such a COS is convincing. A recent survey of 788 Cochrane reviews found that 37% of pre-specified outcomes were not actually reported[198]. A 2012 systematic review and meta-analysis of prepregnancy care for women with pregestational diabetes noted a wide variety in outcomes reported in the included studies[81], a finding that significantly limits interpretation of the results. Additionally, in light of a recent Cochrane review on preconception care for diabetic women advising the need for further high-quality studies in this area[199], it is important that there is guidance on selecting appropriate outcomes for evaluation. This study fills an important gap in the literature, as there is no previously developed COS in the area of prepregnancy care for women with diabetes.

7.5.2 Strengths

This study has a number of strengths. Robust consensus methodology and guidance from the COMET initiative were utilised to develop the COS[210]. A detailed study protocol was published[208] and the COS-STAR statement (appendix 4) was used to ensure clarity and a high standard of reporting[209]. The Delphi process aims to elicit and condense the opinions of many toward consensus. Its function facilitates a large and international participation, and it allows each participant to have an equal voice in rating and suggesting additional outcomes for consideration. The opinion of the participants was that the consensus meeting was collaborative and

inclusive. Prior to altering any outcomes from the Delphi study, significant discussion took place with opinions invited from all participants. The downloadable, electronic application used for anonymous voting prevented individuals feeling pressurised to vote in a certain way.

7.5.3 Limitations and Protocol Deviations

Following the systematic review, the determination of three domains introduced subjectivity in terms of outcome categorisation. A number of independent reviews were taken to reduce this. The study protocol stated that within each domain, outcomes would be listed alphabetically[208]. The intent was to avoid weighting of outcomes caused by the order in which they were displayed. In the actual study, related outcomes were presented alongside each other. The SAG felt that this was more appropriate and would encourage participants to consider overlap between outcomes within domains during the scoring process. In relation to the online survey, the authors acknowledge the risk of nonresponse bias. Due to our sampling approach we do not have an appreciation for the numbers of potential participants who declined to respond, however approximately one third of round 1 participants did not continue on to complete round 3. In addition, while participants came from a variety of backgrounds and countries of residence, the majority were European and in particular, developing countries were not represented.

The final number of outcomes included in the COS may be considered relatively large, however this is related to the nature of prepregnancy care which has potential effects before, during and after pregnancy for two individuals, both mother and child. The authors wish to highlight that in the setting of future randomised controlled trials in this area, we would not expect an inappropriately large number of primary outcomes to be selected, but rather ensure all of these outcomes are collected and reported during the study. Another potential criticism of this study is that it does not provide outcome definitions. It must be specified that the purpose of the COS is to define 'what is to be collected' and not 'how it is to be collected'. In the field of diabetes and pregnancy, there exists a previously

published repository of definitions that may be referenced as required[232]. Finally, it must be acknowledged that a large number of outcomes were carried forward and selected out in the final, consensus meeting phase of the study. During this phase, delegates were chosen to ensure representation from all stakeholder groups and close attention was paid to outcome scores from round 3 of the Delphi prior to excluding any outcome from the COS.

7.5.4 Conclusions

Comparisons between studies evaluating prepregnancy care for women with pregestational diabetes are difficult due to inconsistencies in the approach to collecting and reporting data. This is the first study to define a COS in this area. Its goal is that use of this COS will facilitate international collaboration and allow accurate contrasting and combining of studies. This will make it easier to assess the effect of prepregnancy care, accurately inform policy developers and improve evidence-based practice for women with diabetes.

Chapter 8: The Impact of Pregnancy and Prepregnancy Care on Longer-term Treatment Goals in Women with Type 1 and Type 2 Diabetes

Egan AM, Carmody L, Kirwan B, Dunne FP.
Care of Women with Diabetes Before, During and After Pregnancy – Time for New Approach?
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8.1 Introduction

The increased rate of adverse pregnancy outcomes experienced by women with diabetes can be reduced by optimizing diabetes control[58,67,101,177,178]. Women with diabetes therefore tend to be highly motivated to achieve the tight treatment goals recommended during pregnancy and typically receive intensive education and support from a specialist service[42,43]. Those who attend a prepregnancy care programme benefit from additional multidisciplinary input for approximately six months before pregnancy[101]. Structured prepregnancy care programmes are associated with improved pregnancy preparation and a decrease in adverse pregnancy outcomes, but unfortunately uptake is low[67,101]. Although the attainment of good diabetes control during pregnancy is well described[135], little information exists on measures of glucose control and other diabetes treatment goals post-partum. Furthermore, the ideal approach to postpartum care of women with diabetes is not described. While it may be hypothesised that the skills obtained during prepregnancy and antenatal care programmes will lead to a sustained improvement in treatment targets, limited data from two single-centre studies suggest otherwise[233,234].

8.2 Study Objective

This study assesses the impact of pregnancy and prepregnancy care on longer-term treatment goals in women with diabetes. We hypothesise that an improvement in treatment targets will be observed at 12 months post-partum, particularly in those women who attended prepregnancy care.

8.3 Methods

8.3.1 Study Design

This retrospective study included all women with type 1 or type 2 diabetes attending four centres along the Irish Atlantic Seaboard for antenatal care

between January 2006 and December 2014. The study population contained a mix of urban and rural dwellers. Participants had an established diagnosis of type 1 or type 2 diabetes prior to conception or were diagnosed on the basis of HbA1c greater than 48 mmol/mol (6.5%) in the 1st trimester of pregnancy. The HSE Research Ethics Committee provided ethical approval for the study. In this study, the following variables were evaluated preconceptually (six months prepregnancy or at 1st prepregnancy care visit): weight, blood pressure, smoking status, HbA1c, lipid profile and urinary albumin-creatinine ratio. These variables were re-evaluated at twelve months post-partum. Participant demographics, pregnancy outcomes, mean HbA1c during each trimester of pregnancy and rates of breastfeeding post-partum were also recorded. A detailed account of the prepregnancy care programme was previously described[101]. The programme was freely available to all women with pregestational diabetes across the region. During pregnancy, women attended a combined obstetric-diabetes antenatal care programme and were reviewed every 1-2 weeks by a multi-disciplinary team. Women received education on a number of issues including home glucose monitoring, insulin adjustment and hypoglycaemia management. Prior to discharge from hospital post-partum, women were reviewed by the diabetes team and advised to attend clinic for review at 6 weeks with regular follow up to be scheduled according to clinical need (minimum two visits per year). Attendance at prepregnancy care was advised for those women who were contemplating further pregnancies.

8.3.2 Statistical Analysis

Data were recorded using an optimized digital database, namely DIAMOND (Hicom). Unless otherwise stated, data are expressed as n(%) or mean ± standard deviation of the mean. Hypothesis testing was performed using paired and unpaired t-tests or a non-parametric alternative in the case of non-normally distributed data. χ^2 was used to compare sample proportions. The significance levels was accepted when $\alpha<0.05$ for two-tailed analyses. No permutations were made for missing data.

8.4 Results

8.4.1 Patient Demographics

In total, 384 women were included with a mean age of 32.8 years. Type 1 diabetes was present in 247 (64.3%) and type 2 diabetes in 137 (35.7%).

8.4.2 All participants

Table 1 outlines participant characteristics overall and according to prepregnancy care attendance. The mean preconception HbA1c was 61 mmol/mol (7.7%), and this declined throughout pregnancy with 3rd trimester HbA1c measuring 45 mmol/mol (6.3%). At twelve months post-partum HbA1c had risen to 60 mmol/mol (7.6%) with no significant difference between this and the preconception HbA1c (p= 0.81). There was significant weight gain at twelve months post-partum (73.5 ± 15.6kg versus 77.4 ± 17.7kg, p=0.03). Similar smoking rates were reported post-partum compared to preconceptually (10.7 versus 13.0%, p=0.35), and there was no difference in urinary albumin-creatinine ratio before and after pregnancy (median 0.9 versus 0.9 mg/mmol, p=0.73). There were no differences in low-density lipoprotein (2.8 ± 1.0 versus 2.8 ± 0.9 mmol/L, p=0.50) or triglyceride (1.6 ± 1.5 versus 1.5 ± 1.3 mmol/L, p= 0.38) levels before and twelve months post-partum. High-density lipoprotein levels were slightly lower post-partum (1.8 ± 0.8 versus 1.6 ± 0.5 mmol/L, p=0.03). The post-pregnancy care location varied with 35 (9.1%) participants pregnant and attending combined antenatal clinics, 70 (18.2%) attending prepregnancy care, 195 (50.8%) attending general diabetes clinics in secondary / tertiary care and 84 (21.9%) lost to follow up.

Women who attended prepregnancy care had a lower preconception HbA1c [55 versus 65 mmol/mol (7.2 versus 8.1%, p<0.001]. They maintained this superior glycaemic control throughout each trimester of pregnancy and at twelve months post-partum [56 versus 62 mmol/mol (7.3 versus 7.8%), p=0.02]. They were less likely to be lost to follow up (11.4 versus 28.5%) and more likely to be back in a structured prepregnancy care programme post-partum (28.9 versus 11.5%) (p<0.001). Despite

having similar weights preconception, those women who attended prepregnancy care had a lower weight post-partum (74.6 ± 15.3 versus 79.6 ± 19.1kg, p=0.03). Attendees also had a lower systolic blood pressure (119.9 ± 16.4 versus 125.9 ± 15.4mmHg, p=0.01) and urine albumin creatinine ratio (median 0.8 versus 1.1mg/mmol, p=0.01) post-partum.

8.4.3 Women with Type 1 Diabetes

Table 8.2 outlines the characteristics of those participants with type 1 diabetes. The majority of participants were of White European ethnicity (n=246, 99.6%) and the average duration of diabetes was 14.5 years. The mean preconception HbA1c was 64mmol/mol (8.0%) and this declined throughout each trimester of pregnancy. At 12 months post-partum, the mean HbA1c was 63mmol/mol (7.9%) with no difference between this and the preconception HbA1c (p=0.60). Participants experienced a non-significant increase in weight post-partum (69.0 versus 70.8kg, p=0.06). A significant number of women were no longer smoking at the post-partum review (14.6 versus 10.1%, p=0.01). Women were cared for in a variety of locations post-partum, and 53 (21.5%) participants were lost to follow up.

Those who attended prepregnancy care (n=111, 44.9%) had a lower preconception HbA1c [57 versus 76mmol/mol (7.4 versus 9.1%), p<0.001]. They maintained superior glycaemic control throughout each trimester of pregnancy and this was sustained at 12 months post-partum [57 versus 69mmol/mol (7.4 versus 8.5%), p<0.001]. Women who attended prepregnancy care were less likely to be smoking preconceptually (7.2 versus 20.6%, p=0.003) or post-partum (3.6 versus 16.3%, p=0.004). Finally they were less likely to be lost to follow up at 12 months post-partum (10.8 versus 30.1%, p<0.001).

Table 8.1: Participant Characteristics Overall and According to Prepregnancy Care Attendance

	Whole group	Pre-pregnancy Care	No pre-pregnancy Care	P Value (pre-pregnancy care versus none)
Number of subjects (n)(% total)	384 (100.0)	149 (38.8)	235 (61.2)	
Age (years)	32.8 ± 5.4	33.8 ± 4.6	32.1 ± 5.7	0.001
Caucasian ethnicity (n)(%)	344 (89.6)	143 (96.0)	201 (85.5)	0.001
Type 1 diabetes	247 (64.3)	111 (74.5)	136 (57.9)	
Type 2 diabetes	137 (35.7)	38 (25.5)	99 (42.1)	0.001
Preconception weight (kg)	73.5 ± 15.6	72.6 ± 14.2	74.9 ± 17.6	0.38
Preconception SBP (mmHg)	123.5 ± 14.3	124.1 ± 13.3	122.4±15.9	0.49
Preconception DBP (mmHg)	75.8 ± 9.2	76.4 ± 7.8	74.3 ± 11.0	0.13
Preconception urine ACR (mg/mmol)[a]	0.9 (1.8)	0.8 (1.5)	1.2 (5.7)	0.31
Preconception smoking	50 (13.0)	13 (8.7)	37 (15.7)	0.04
Preconception LDL (mmol/L)	2.8 ± 1.0	2.7 ± 0.9	2.9 ± 1.0	0.23
Preconception triglycerides (mmol/L)	1.6 ± 1.5	1.5 ± 1.2	1.7 ± 1.9	0.48
Preconception HDL	1.8 ± 0.8	1.9 ± 0.8	1.7 ± 0.7	0.33
Preconception HbA1c (mmol/mol) (%)	61 ± 22 (7.7 ± 2.0)	55 ± 14 (7.2 ± 1.3)	65 ± 27 (8.1 ± 2.5)	<0.001
1st trimester HbA1c (mmol/mol) (%)	56 ± 17 (7.3 ± 1.6)	51 ± 13 (6.8 ± 1.2)	60 ± 20 (7.6 ± 1.8)	<0.001
2nd trimester HbA1c (mmol/mol) (%)	46 ± 11 (6.4 ± 1.0)	44 ± 8 (6.2 ± 0.7)	49 ± 12 (6.6 ± 1.1)	<0.001
3rd trimester HbA1c(mmol/mol) (%)	45 ± 10 (6.3 ± 0.9)	43 ± 8 (6.1 ± 0.7)	46 ± 11 (6.4 ± 1.0)	0.01
Birth Outcome: Livebirth (n)(%)	315 (82.0)	122 (81.9)	193 (82.1)	
Miscarriage (n)(%)	59 (15.4)	25 (16.8)	34 (14.5)	
Stillbirth (n)(%)	10 (2.6)	2 (1.3)	8 (3.4)	
Neonatal death	0	0	0	0.41
Breastfeeding	126 (32.8)	54 (36.2)	72 (30.6)	0.52
Care location 12 months post-partum				
Pregnant at review (n)(%)	35 (9.1)	20 (13.4)	15 (6.4)	
Prepregnancy care (n)(%)	70 (18.2)	43 (28.9)	27 (11.5)	
General diabetes clinic (n)(%)	195 (50.8)	69 (46.3)	126 (53.6)	
Lost to follow up (n)(%)	84 (21.9)	17 (11.4)	67 (28.5)	<0.001
	n=300[b]	n=132[b]	n=168[b]	
Post-partum weight (kg)	77.4 ± 17.7	74.6 ± 15.3	79.6 ± 19.1	0.03
Post-partum SBP (mmHg)	123.2 ± 16.1	119.9 ± 16.4	125.9±15.4	0.01
Post-partum DBP (mmHg)	75.3 ± 9.6	74.9 ± 8.1	75.6 ± 10.8	0.56
Post-partum urine ACR (mg/mmol)*	0.9 (1.9)	0.8 (1.4)	1.1 (2.8)	0.01
Post-partum smoking (n)(%)	32 (10.7)	9 (6.8)	23 (13.7)	0.06
Post-partum LDL (mmol/L)	2.8 ± 0.9	2.7 ± 0.9	2.9 ± 0.9	0.30
Post-partum triglycerides (mmol/L)	1.5 ± 1.3	1.3 ± 1.0	1.6 ± 1.4	0.09
Post-partum HDL (mmol/L)	1.6 ± 0.5	1.6 ± 0.5	1.5 ± 0.5	0.11
Post-partum HbA1c (mmol/mol) (%)	60 ± 20 (7.6 ± 1.8)	56 ± 14 (7.3 ± 1.3)	62 ± 23 (7.8 ± 2.1)	0.02

Data are expressed as n(%) or mean ± standard deviation unless otherwise stated. [a]data expressed median and interquartile range (not normally distributed). [b]excludes those subjects pregnant at review and lost to follow up. SBP: systolic blood pressure; DPB: diastolic blood pressure; ACR: albumin-creatinine ratio; LDL: low density lipoprotein; HDL: high density lipoprotein.

Table 8.2: Participants with Type 1 Diabetes: Characteristics Overall and According to Prepregnancy Care Attendance

	Whole group	Pre-pregnancy Care	No pre-pregnancy Care	P Value (pre-pregnancy care versus none)
Number of subjects (n)(% total)	247 (100.0)	111 (44.9)	136 (55.0)	
Age (years)	32.4 ± 5.5	34.0 ± 4.9	31.0 ± 5.7	<0.001
White European ethnicity (n)(%)	246 (99.6)	111 (100.0)	135 (99.3)	0.37
Duration of diabetes (years)	14.5 ± 8.6	14.7 ± 9.4	14.4 ± 8.0	0.75
Preconception weight (kg)	69.0 ± 12.7	68.7 ± 10.8	69.6 ± 15.4	0.75
Preconception SBP (mmHg)	122.8 ± 15.0	124.2 ± 14.2	120.4 ± 16.0	0.17
Preconception DBP (mmHg)	74.8 ± 9.3	76.3 ± 8.3	72.2 ± 10.4	0.02
Preconception urine ACR (mg/mmol)[a]	0.8 (1.9)	0.7 (1.3)	1.3 (7.7)	0.10
Preconception smoking	36 (14.6)	8 (7.2)	28 (20.6)	0.003
Preconception LDL (mmol/L)	2.7 ± 0.9	2.8 ± 0.9	2.7 ± 1.0	0.83
Preconception triglycerides (mmol/L)	1.4 ±1.4	1.4 ± 1.0	1.7 ± 2.2	0.33
Preconception HDL	2.0 ± 0.8	2.0 ± 0.8	2.0 ± 0.7	0.93
Preconception HbA1c (mmol/mol) (%)	64 ± 21 (8.0 ± 1.9)	57 ± 13 (7.4 ± 1.2)	76 ± 25 9.1 ± 2.3	<0.001
1st trimester HbA1c (mmol/mol) (%)	59 ± 18 (7.5 ± 1.6)	52 ± 11 (6.9 ± 1.0)	65 ± 20 (8.1 ± 1.8)	<0.001
2nd trimester HbA1c (mmol/mol) (%)	49 ± 12 (6.6 ± 1.1)	45 ± 9 (6.3 ± 0.8)	52 ± 13 (6.9 ± 1.2)	<0.001
3rd trimester HbA1c (mmol/mol) (%)	48 ± 11 (6.5 ± 1.0)	44 ± 7.7 (6.2 ± 0.7)	51 ± 12 (6.8 ± 1.1)	0.001
Birth Outcome: Livebirth (n)(%)	195 (78.9)	88 (79.3)	107 (78.7)	
Miscarriage (n)(%)	44 (17.8)	21 (18.9)	23 (16.9)	
Stillbirth (n)(%)	8 (3.2)	2 (1.8)	6 (4.4)	
Neonatal death	0 (0)	0 (0)	0 (0)	0.49
Breastfeeding	79 (32)	39 (35.1)	40 (29.4)	0.63
Care location 12 months post-partum				
Pregnant at review (n)(%)	25 (10.1)	16 (14.4)	9 (6.6)	
Prepregnancy care (n)(%)	49 (19.8)	34 (30.6)	15 (11.0)	
General diabetes clinic (n)(%)	120 (48.6)	49 (44.1)	71 (52.2)	
Lost to follow up (n)(%)	53 (21.5)	12 (10.8)	41 (30.1)	<0.001
	n=169[b]	n=83[b]	n=86[b]	
Post-partum weight (kg)	70.8 ± 30.5	70.0 ± 12.4	71.7 ± 14.6	0.46
Post-partum SBP (mmHg)	121.4 ± 16.8	119.2 ± 17.5	123.7 ± 15.7	0.10
Post-partum DBP (mmHg)	74.4 ± 10.3	74.2 ± 8.4	74.5 ± 12.0	0.88
Post-partum urine ACR (mg/mmol)[a]	0.9 (2.0)	0.7 (1.7)	1.2 (7.1)	0.03
Post-partum smoking (n)(%)	17 (10.1)	3 (3.6)	14 (16.3)	0.004
Post-partum LDL (mmol/L)	2.7 ± 0.9	2.6 ± 0.9	2.9 ± 0.9	0.21
Post-partum triglycerides (mmol/L)	1.2 ± 1.2	1.1 ± 1.0	1.4 ± 1.3	0.28
Post-partum HDL (mmol/L)	1.8 ± 0.5	1.8 ± 0.5	1.8 ± 0.5	0.99
Post-partum HbA1c (mmol/mol) (%)	63 ± 21 (7.9 ± 1.9)	57 ± 13 (7.4 ± 1.2)	69 ± 25 (8.5 ± 2.3)	<0.001

Data are expressed as n(%) or mean ± standard deviation unless otherwise stated. [a]data expressed median and interquartile range (not normally distributed). [b]excludes those subjects pregnant at review and lost to follow up. SBP: systolic blood pressure; DPB: diastolic blood pressure; ACR: albumin-creatinine ratio; LDL: low density lipoprotein; HDL: high density lipoprotein.

8.4.4 Women with Type 2 Diabetes

Table 8.3 outlines the characteristics of those participants with type 2 diabetes. The average duration of diabetes was 2.7 years and 98 (71.5%) women were of White European ethnicity. The mean preconception HbA1c was 52mmol/mol (6.9%) and this declined during pregnancy with a mean 3rd trimester HbA1c of 42mmol/mol (6.0%). At 12 months post-partum, HbA1c was similar to prepregnancy levels at 52mmol/mol (6.9%) (p=0.79). Women with type 2 diabetes experienced a non-significant increase in weight at 12 months post-partum (86.6 versus 90.6kg, p=0.30). There was no significant difference in smoking rates before and after pregnancy (10.2 versus 15.6%, p=0.23), although one participant had taken up smoking at the time of post-partum review.

In total, 38 (27.7%) participants with type 2 diabetes attended prepregnancy care. They were more likely to be of White European ethnicity (84.2% versus 66.7%, p=0.04). Women who attended prepregnancy care had a lower preconception HbA1c [46 versus 59mmol/mol (6.4 versus 7.5%), p=0.04]. This difference was evident throughout the 1st and 2nd trimesters of pregnancy but there was no difference in HbA1c between groups in the 3rd trimester of pregnancy [41 versus 43mmol/mol (5.9 versus 6.1%), p=0.29] or post-partum [53 versus 52mmol/mol (7.0 versus 6.9%), p=0.74)].

Table 8.3: Participants with type 2 diabetes: characteristics overall and according to prepregnancy care attendance

	Whole group	Pre-pregnancy Care	No pre-pregnancy Care	P Value (pre-pregnancy care versus none)
Number of subjects (n)(% total)	137 (100.0)	38 (27.7)	99 (72.3)	
Age (years)	33.5 ± 4.9	33.3 ± 3.5	33.6 ± 5.4	0.78
White European ethnicity (n)(%)	98 (71.5)	32 (84.2)	66 (66.7)	0.04
Duration of diabetes (years)	2.7 ± 3.9	2.8 ± 2.5	2.7 ± 4.3	0.81
Preconception weight (kg)	86.6 ± 16.0	84.4 ± 16.9	90.4 ± 14.4	0.27
Preconception SBP (mmHg)	125.5 ± 12.1	123.7 ± 10.4	128.4 ± 14.4	0.24
Preconception DBP (mmHg)	78.8 ± 8.0	77.8 ± 5.9	77.3 ± 8.4	0.36
Preconception urine ACR (mg/mmol)[a]	0.8 (1.4)	0.8 (1.4)	0.7 (1.4)	0.32
Preconception smoking	14 (10.2)	5 (13.2)	9 (9.1)	0.48
Preconception LDL (mmol/L)	2.9 ± 1.0	2.6 ± 0.9	3.3 ± 0.9	0.04
Preconception triglycerides (mmol/L)	2.0 ± 1.4	2.1 ± 1.5	1.8 ± 1.2	0.63
Preconception HDL	1.3 ± 0.3	1.4 ± 0.4	1.3 ± 0.3	0.36
Preconception HbA1c (mmol/mol) (%)	52 ± 21	46 ± 13	59 ± 27	
	6.9 ± 1.9	6.4 ± 1.2	7.5 ± 2.5	0.04
1st trimester HbA1c (mmol/mol) (%)	50 ± 18	45 ± 16	52 ± 19	
	6.7 ± 1.6	6.3 ± 1.5	6.9 ± 1.7	0.09
2nd trimester HbA1c (mmol/mol) (%)	42 ± 18	39 ± 5.5	43 ± 8	
	6.0 ± 1.6	5.7 ± 0.5	6.1± 0.7	0.004
3rd trimester HbA1c (mmol/mol) (%)	42 ± 7	41 ± 7	43 ± 8	
	6.0 ± 0.6	5.9 ± 0.6	6.1 ± 0.7	0.29
Birth Outcome: Livebirth (n)(%)	120 (97.6)	34 (89.5)	86 (86.9)	
Miscarriage (n)(%)	15 (10.9)	4 (10.5)	11(11.1)	
Stillbirth (n)(%)	2 (1.5)	0 (0)	2 (2.0)	
Neonatal death	0 (0)	0 (0)	0 (0)	0.67
Breastfeeding	47 (34.3)	15 (39.5)	32 (32.3)	0.73
Care location 12 months post-partum				
Pregnant at review (n)(%)	10 (7.3)	4 (10.5)	6 (6.1)	
Prepregnancy care (n)(%)	21 (15.3)	9 (23.7)	12 (12.1)	
General diabetes clinic (n)(%)	75 (54.7)	20 (52.6)	55 (55.6)	
Lost to follow up (n)(%)	31 (22.6)	5 (13.2)	26 (26.3)	0.15
	n=96[b]	n=29[b]	n=67[b]	
Post-partum weight (kg)	90.6 ± 17.8	89.3 ± 14.8	91.3 ± 19.1	0.65
Post-partum SBP (mmHg)	125.7 ± 15.3	122.8 ± 11.5	126.9 ± 16.4	0.04
Post-partum DBP (mmHg)	75.0 ±10.4	75.6 ± 9.1	74.7 ± 11.0	0.76
Post-partum urine ACR (mg/mmol)[a]	0.9 (2.4)	0.9 (5.2)	1.4 (2.7)	0.29
Post-partum smoking (n)(%)	15 (15.6)	6 (20.1)	9 (13.4)	0.45
Post-partum LDL (mmol/L)	2.9 ± 1.0	2.9 ± 1.0	2.9 ± 0.9	0.84
Post-partum triglycerides (mmol/L)	1.9 ± 1.3	1.8 ± 0.9	1.9 ± 1.5	0.87
Post-partum HDL (mmol/L)	1.3 ± 0.4	1.4 ± 0.4	1.3 ± 0.3	0.48
Post-partum HbA1c (mmol/mol) (%)	52 ± 14	53 ± 16	52 ± 13	
	6.9 ± 1.3	7.0 ± 1.5	6.9 ± 1.2	0.74

Data expressed as n (%) and mean ± standard deviation unless otherwise stated. [a]data expressed median and interquartile range (not normally distributed). [b]excludes those subjects pregnant at review and lost to follow up. SBP: systolic blood pressure; DPB: diastolic blood pressure; ACR: albumin-creatinine ratio; LDL: low density lipoprotein; HDL: high density lipoprotein.

8.5 Discussion

8.5.1 Summary and Discussion of Findings

In this study consistent with our findings in chapter 5, despite a freely available prepregnancy care programme, just 44.9% of women with type 1 diabetes and 27.7% of those with type 2 diabetes attended. Although the participants all engaged in an intensive diabetes management programme during pregnancy, there was no improvement in measures of diabetes control post-partum and 1 in 5 women are lost to follow up from clinical care. Overall participants experienced a progressive improvement in HbA1c during pregnancy. This is likely due to a combination of more intensive diabetes management and the known effect of increased red cell turnover during pregnancy[235]. At 12 months post-partum HbA1c was similar to prepregnancy levels. Women who attended prepregnancy care however, maintained superior glycaemic control throughout the study and were more likely to be receiving specialist care post-partum.

Our data highlight the importance of universal access to prepregnancy care and the need to overcome known barriers to attendance[82,83]. Although those that attend are likely a more self-motivated group from the outset, we have previously demonstrated that it is possible to increase attendance using a systematic, population-based approach (chapter 5)[101]. Our findings of overall poor pregnancy preparation are reflected in the 2015 National Pregnancy in Diabetes Audit in the UK. It reported that just 46% of women with type 1 diabetes and 23% of those with type 2 diabetes were taking 5mg folic acid prepregnancy, and only 16% women with type 1 diabetes and 38% women with type 2 diabetes had a 1st trimester HbA1c <48mmol/mol (6.5%).[63] It is clear that recruitment efforts should aim to encourage women with type 2 diabetes and those from ethnic minorities to attend. In particular, any language barriers affecting delivery of care to the latter group should be identified and managed appropriately.

There are two previous studies in the area of post-partum care, both of which are smaller, single-centre and include women with type 1 diabetes

only[233,234]. This current study confirms their findings of a post-partum deterioration in glycaemic control and demonstrates that this issue is applicable to a larger, regional population of women with both type 1 and type 2 diabetes. Our data also reveal a similar post-partum weight retention. The weight changes do not reach significance in the diabetes subgroups in our study and this may be related to sample size. This finding is also noted in women without diabetes, with a mean weight gain from prepregnancy to 1 year follow up of 1.4kg reported in one large study[236]. It is very clear that our current approach to post-partum care is not adequate and specific action is required to support women in this critical period. Possible challenges to address include poor motivation to continue intensive self-management post-pregnancy and the busy lifestyle involved in looking after an infant.

8.5.2 Strengths

This is the first study to assess the impact of pregnancy and prepregnancy care on longer-term treatment goals in a regional cohort of women with type 1 and type 2 diabetes. Detailed patient-level data are presented and robust statistical techniques are used to compare variables before and after pregnancy and women who did and did not attend prepregnancy care.

8.5.3 Limitations

Limitations of this study include its retrospective nature and lack of information on women who were lost to follow up. In Ireland, people with pregestational diabetes are not typically managed in primary care so it is likely that these women were not receiving any form of diabetes care. We were unable to adjust our analysis for the effects of socioeconomic status, a variable that is difficult to measure in the context of the mixed urban-rural characteristics of the population.

8.5.4 Conclusions

In conclusion, these findings challenge healthcare providers to develop and evaluate strategies to engage women prepregnancy and to encourage them to utilize the self-management skills obtained and practiced during

pregnancy post-partum. A new approach to the post-partum care of women with diabetes is required, with the aim of improving overall health in this population.

Chapter 9: Discussion and Conclusions

Pregestational diabetes is the most common chronic medical condition to complicate pregnancy and is associated with significant risk to both mother and infant. Even in developed countries with structured healthcare systems, complications such as foetal macrosomia continue to affect up to 50% infants born to women with established diabetes[57,64,66]. In Ireland and the United Kingdom devastating outcomes including congenital anomalies and stillbirths still remain well above the population average[63,135]. Prevention of morbidity and mortality in this population of women and children is clearly an important public health issue.

In this thesis, I examined a cohort of women with type 1 and type 2 diabetes residing in the West of Ireland. With an average of 11,000 births per year, this region is composed of approximately 500,000 urban and rural dwellers and is home to the Atlantic DIP initiative. This initiative consists of motivated health care professionals aiming to improve outcomes for women with diabetes in pregnancy through research and delivery of an evidence-based clinical programme.

In the first study of this thesis, pregnancies in women with type 1 and type 2 diabetes were evaluated over a ten-year period. This analysis revealed an improvement in outcomes following a change in the process of clinical care delivery. The next two studies identify areas that require further work in terms of this care delivery– that is prevention of excessive GWG and management of diabetic retinopathy in pregnancy. Subsequently, the benefits of prepregnancy care for women with diabetes are clearly described in a prospective cohort study and a COS for studies evaluating the effectiveness of prepregnancy care is developed. The final study highlights a paucity of data on the best approach to care for women with diabetes post-partum and the need to engage women during this important time.

Overall, this thesis highlights the importance of a continuum of care for women with type 1 and type 2 diabetes before, during and after pregnancy. The approach taken by the Atlantic DIP initiative can serve as an adaptable

template for healthcare professionals to support a global move towards better outcomes for these women and their offspring. Importantly, areas ripe for improvement in clinical care are also highlighted as described in the following chapter summaries.

Chapter 2

In this study 445 pregnancies in women with type 1 and type 2 diabetes were examined and compared over two time points 2005-2009 and 2010-2014. A number of regional interventions were in place for the latter half of the study. These included provision of combined antenatal/diabetes clinics, a structured prepregnancy care programme, electronic data management, local clinical care guidelines and patient/heathcare professional education materials including a downloadable application and a website. I collated the patient level data and completed the univariate statistical analysis to examine for differences in outcomes across the two time points. I worked closely with my colleague Dr Lisa Owens to present these data and interpret the findings. We report an increase in attendance at prepregnancy care (23 to 49%; $p<0.001$), use of folic acid (45 versus 71%; $p<0.001$), and an improvement in glycaemic control during pregnancy. We observe an upward trend in maternal age, obesity rates and excessive GWG.

Chapter 3

Excessive GWG is a risk factor for maternofoetal complications and in 2009 the IOM published recommendations for appropriate GWG[87,136-138]. It remained unclear however, if these guidelines are applicable to the already at-risk population of women with diabetes. In this observational study I evaluated 802 women with diabetes in pregnancy, calculated mean weight gain per week and compared with IOM guidelines to assess if the upper limit of recommended weight gain as per BMI category was breached (table 1.1). Maternal and foetal outcomes were then evaluated

using univariate and multivariate analyses. Excessive GWG was noted in 59%. Among women with type 1 and type 2 diabetes (n=259) excessive GWG was found to be an independent risk factor for LGA (aOR 3.97) and macrosomia (aOR 3.58). For comparison, this study included a cohort of women with GDM (n=543) who were found to have increased risk of LGA (aOR 2.01), macrosomia (aOR 2.17) and gestational hypertension (aOR 1.72) in the setting of excessive GWG. This study confirms that GWG in excess of IOM recommendations confers an additive risk of adverse outcomes for women with diabetes in pregnancy.

Chapter 4

In this study, I explored the issue of diabetic retinopathy in pregnancy in more detail. Deterioration of retinopathy is well described in women with pregestational diabetes[59,60] but there are no previously published regional or national data on this subject. A total of 307 women with type 1 and type 2 diabetes were included. I assessed the frequency of retinal examination during pregnancy and identified women experiencing progression of the condition. In total, 185 (60.3%) had an adequate number of retinal examinations. Attendance at prepregnancy care was associated with receiving adequate screening (aOR 6.23). Among those who received adequate evaluations, 48 (25.9%) had retinopathy progression. Increasing booking systolic blood pressure (aOR 1.03) and greater drop in HbA1c between 1st and 3rd trimesters of pregnancy (OR 2.05) significantly increased the odds of progression. This study highlights the importance of a structured approach to monitoring women for progression of diabetic retinopathy during pregnancy and identifies risk factors for progression.

Chapter 5

In this chapter, I describe the clinical and economic benefits of a regional prepregnancy care programme for women with type 1 and type 2 diabetes. This prospective cohort and cost-analysis study was completed in conjunction with the Atlantic DIP collaborators. I collated the patient-level data and completed a robust statistical analysis of pregnancy outcomes for those who did and did not attend prepregnancy care. I collaborated with my colleague Dr Andriy Danyliv (School of Economics, National University of Ireland Galway) to complete a detailed analysis defining the cost of delivery of prepregnancy care. This was compared to the excess cost of managing adverse pregnancy outcomes in those women who did not attend. In total, 149 (36%) attended: this increased from 19% to 50% after increased recruitment measures in 2010. Attendees were better prepared for pregnancy and their offspring had lower rates of serious adverse outcomes (2.4% versus 10.5%, p = .007). The adjusted difference in complication costs between those who received prepregnancy care versus usual antenatal care only is €2578.00. The average cost of prepregnancy care delivery is €449.00 per pregnancy. This study confirms the clinical effectiveness of a regional approach to prepregnancy care and highlights the associated economic benefits. Due to these findings, prepregnancy care is now freely available to all women with diabetes in the region.

Chapter 6

While researching the area of prepregnancy care for women with diabetes, I observed significant heterogeneity in the outcomes measured and reported in previously published studies. This limits the comparing and contrasting of studies acts as a barrier to combining studies for the purposes of meta-analyses. I therefore designed a protocol for a study to develop a COS for trials and other studies evaluating the effectiveness of prepregnancy care for women with pregestational diabetes. This chapter

describes in detail the following steps necessary to develop the COS: (i) a systematic literature review to identify all previously reported outcomes and (ii) prioritisation of these outcomes from the perspective of key stakeholders using a Delphi survey and consensus meeting. The chapter contains a detailed outline of all the practical and statistical methods and approaches necessary to complete the process.

Chapter 7

Following on directly from chapter 6, this chapter describes the development of a COS for trials and other studies evaluating the effectiveness of prepregnancy care for women with pregestational diabetes. I developed the systematic review question, designed and completed the electronic search strategies and extracted relevant data. Working with collaborators (Prof Declan Devane and Dr Valerie Smith, School of Nursing and Midwifery), 33 relevant papers were included and 86 individual outcomes identified. These outcomes were presented to participants over 3 rounds of a Delphi study that I directed and analysed. The final phases of the study involved a consensus meeting using a downloadable application where an international group of participants voted on which outcomes to include in the final COS. The final COS consists of 17 outcomes across three domains (measures of pregnancy preparation, neonatal outcomes and maternal outcomes). It is our goal that use of this COS will facilitate international collaboration and allow accurate contrasting and combining of studies to assess the effect of prepregnancy care programmes. This will have the downstream effect of accurately informing clinicians and policy makers on ways to deliver and improve delivery of this important service.

Chapter 8

The final study in this thesis assesses the impact of pregnancy and prepregnancy care on longer-term treatment goals in women with type 1 and type 2 diabetes. While it was hypothesised that the skills obtained during prepregnancy and antenatal care programmes would result in a sustained improvement in treatment targets such as HbA1c, we found no such benefit. In fact, 1 in 5 participants were lost to follow up from clinical care at 12 months post-partum. For the purposes of this study, I collected and analysed detailed patient-level data from a number of databases. A clear gap in patient care is identified and the need to modify our entire approach to post-partum care is highlighted.

Future Directions

In conclusion, type 1 and type 2 diabetes are associated with an increased risk of adverse pregnancy outcomes. This thesis outlines how a structured approach to clinical care based on sound evidence has the potential to improve these outcomes across an entire region. It is hoped that our findings will influence national and international policy to make prepregnancy and combined obstetric-diabetes antenatal care available to all women with diabetes.

Specific areas requiring further research include the development and application of novel technologies to help women achieve better glucose control, and new approaches to modify GWG and reduce foetal overgrowth. Further work is required in designing prepregnancy and post-partum clinical care programmes to move towards universal attendance, particularly in women with type 2 diabetes and those from minority groups who are currently less likely to attend. These programmes will need to address the specific needs of the population they serve, in our case a cohort with an increasing maternal age and obesity rate.

References

1. Laios K, Karamanou M, Saridaki Z, Androutsos G. Aretaeus of Cappadocia and the first description of diabetes. *Hormones (Athens).* 2012;11(1):109-113.
2. Adams F. *The extant works of Aretaeus the Cappadocian.* London: Sydenham Society; 1856.
3. Ahmed AM. History of diabetes mellitus. *Saudi Med J.* 2002;23(4):373-378.
4. Karamanou M, Protogerou A, Tsoucalas G, Androutsos G, Poulakou-Rebelakou E. Milestones in the history of diabetes mellitus: The main contributors. *World J Diabetes.* 2016;7(1):1-7.
5. Willis T. *Opera Omnia. Coloniae: Sumptibus Gasparis Storti.* Leiden: Brill; 1694.
6. von Mering J, Minkowski O. Diabetes mellitus nach Pankreas extirpation. *Arch f exper Path u Pharmakol.* 1889;26:371.
7. Banting FG, Best CH, Collip JB, Campbell WR, Fletcher AA. Pancreatic Extracts in the Treatment of Diabetes Mellitus. *Can Med Assoc J.* 1922;12(3):141-146.
8. Banting F, Best C, Collip J, et al. The Effect Produced on Diabetes by Extractions of Pancreas. *Transact Ass Amer Physicians.* 1922;37:337.
9. Banting F, Best C, Mcleod J. The internal secretion of the pancreas. *Amer J Physiol.* 1922;59:479.
10. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care.* 2014;37 Suppl 1:S81-90.
11. Egan A, Dinneen S. What is diabetes? *Medicine.* 2014;42(12):679-681.
12. Newton CA, Raskin P. Diabetic ketoacidosis in type 1 and type 2 diabetes mellitus: clinical and biochemical differences. *Arch Intern Med.* 2004;164(17):1925-1931.

13. Jacobs J, Sena M, Fox N. The cost of hospitalization for the late complications of diabetes in the United States. *Diabet Med.* 1991;8 Spec No:S23-29.
14. Andersen AR, Christiansen JS, Andersen JK, Kreiner S, Deckert T. Diabetic nephropathy in Type 1 (insulin-dependent) diabetes: an epidemiological study. *Diabetologia.* 1983;25(6):496-501.
15. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N Engl J Med.* 1993;329(14):977-986.
16. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. *N Engl J Med.* 2000;342(6):381-389.
17. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet.* 1998;352(9131):837-853.
18. American Diabetes Association. 2. Classification and Diagnosis of Diabetes. *Diabetes Care.* 2017;40(Suppl 1):S11-S24.
19. Eisenbarth GS. Update in type 1 diabetes. *J Clin Endocrinol Metab.* 2007;92(7):2403-2407.
20. Smushkin G, Vella A. What is type 2 diabetes? *Medicine (Abingdon).* 2010;38(11):597-601.
21. Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy: a World Health Organization Guideline. *Diabetes Res Clin Pract.* 2014;103(3):341-363.
22. O'Sullivan EP, Avalos G, O'Reilly M, et al. Atlantic Diabetes in Pregnancy (DIP): the prevalence and outcomes of gestational diabetes mellitus using new diagnostic criteria. *Diabetologia.* 2011;54(7):1670-1675.
23. O'Dea A, Tierney M, McGuire BE, et al. Can the Onset of Type 2 Diabetes Be Delayed by a Group-Based Lifestyle Intervention in

Women with Prediabetes following Gestational Diabetes Mellitus (GDM)? Findings from a Randomized Control Mixed Methods Trial. *J Diabetes Res.* 2015;2015:798460.

24. Metzger BE, Bybee DE, Freinkel N, Phelps RL, Radvany RM, Vaisrub N. Gestational diabetes mellitus. Correlations between the phenotypic and genotypic characteristics of the mother and abnormal glucose tolerance during the first year postpartum. *Diabetes.* 1985;34 Suppl 2:111-115.
25. O'Sullivan JB. Subsequent morbidity among gestational diabetic women. *Sutherland HW, Stowers JM (meds). Carbohydrate Metabolism in Pregnancy and the Newborn.* Churchill Livingstone: Edinburgh; 1984.
26. Kim C, Newton KM, Knopp RH. Gestational diabetes and the incidence of type 2 diabetes: a systematic review. *Diabetes Care.* 2002;25(10):1862-1868.
27. Stride A, Hattersley AT. Different genes, different diabetes: lessons from maturity-onset diabetes of the young. *Ann Med.* 2002;34(3):207-216.
28. International Expert Committee. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. *Diabetes Care.* 2009;32(7):1327-1334.
29. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care.* 1997;20(7):1183-1197.
30. World Health Organization. *Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications: Report of a WHO Consultation. Part 1: Diagnosis and Classification of Diabetes Mellitus.* Geneva; 1999.
31. McCance DR, Hanson RL, Charles MA, et al. Comparison of tests for glycated haemoglobin and fasting and two hour plasma glucose concentrations as diagnostic methods for diabetes. *BMJ.* 1994;308(6940):1323-1328.
32. Nathan DM, Turgeon H, Regan S. Relationship between glycated haemoglobin levels and mean glucose levels over time. *Diabetologia.* 2007;50(11):2239-2244.

33. Massi-Benedetti M. Changing targets in the treatment of type 2 diabetes. *Curr Med Res Opin.* 2006;22 Suppl 2:S5-13.
34. Hoelzel W, Weykamp C, Jeppsson JO, et al. IFCC reference system for measurement of hemoglobin A1c in human blood and the national standardization schemes in the United States, Japan, and Sweden: a method-comparison study. *Clin Chem.* 2004;50(1):166-174.
35. Goldstein DE, Little RR, Lorenz RA, et al. Tests of glycemia in diabetes. *Diabetes Care.* 2004;27(7):1761-1773.
36. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care.* 2010;33 Suppl 1:S62-69.
37. World Health Organization. *Use of glycated haemoglobin (HbA1c) in the diagnosis of diabetes mellitus. Abbreviated report of a WHO consultation.* Geneva; 2011.
38. Bry L, Chen PC, Sacks DB. Effects of hemoglobin variants and chemically modified derivatives on assays for glycohemoglobin. *Clin Chem.* 2001;47(2):153-163.
39. Gallagher EJ, Le Roith D, Bloomgarden Z. Review of hemoglobin A(1c) in the management of diabetes. *J Diabetes.* 2009;1(1):9-17.
40. Benhalima K, Mathieu C, Damm P, et al. A proposal for the use of uniform diagnostic criteria for gestational diabetes in Europe: an opinion paper by the European Board & College of Obstetrics and Gynaecology (EBCOG). *Diabetologia.* 2015;58(7):1422-1429.
41. Metzger BE, Gabbe SG, Persson B, et al. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care.* 2010;33(3):676-682.
42. National Institute of Health and Care Excellence (NICE). *Diabetes in pregnancy: management from preconception to the postnatal period.* 2015. https://www.nice.org.uk/guidance/ng3. Accessed January 23rd 2017.
43. American DiabetesAssociation. 13. Management of Diabetes in Pregnancy. *Diabetes Care.* 2017;40(Suppl 1):S114-S119.

44. Health Service Executive. *Guidelines for the Management of Pre-gestational and Gestational Diabetes Mellitus from Pre-conception to the Postnatal period.* 2010. http://www.hse.ie/eng/services/publications/NursingMidwiferyServices/onsdguidelinesgestationaldiabetes.pdf. Accessed January 23rd 2017.

45. Blumer I, Hadar E, Hadden DR, et al. Diabetes and pregnancy: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab.* 2013;98(11):4227-4249.

46. Hod M, Kapur A, Sacks DA, et al. The International Federation of Gynecology and Obstetrics (FIGO) Initiative on gestational diabetes mellitus: A pragmatic guide for diagnosis, management, and care. *Int J Gynaecol Obstet.* 2015;131 Suppl 3:S173-211.

47. Carpenter MW, Coustan DR. Criteria for screening tests for gestational diabetes. *Am J Obstet Gynecol.* 1982;144(7):768-773.

48. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. National Diabetes Data Group. *Diabetes.* 1979;28(12):1039-1057.

49. National Institute for Health and Care Excellence (NICE). *Type 1 diabetes in adults overview*. 2016. https://www.nice.org.uk/guidance/ng17. Accessed January 23rd 2017

50. Dunne FP, Gaffney G, collaborators AD. The birth of ATLANTIC DIP: an overview. *Ir Med J.* 2012;105(5 Suppl):2-4.

51. McCance DR. Diabetes in pregnancy. *Best Pract Res Clin Obstet Gynaecol.* 2015;29(5):685-699.

52. Noctor E. *The prevalence of abnormal glucose tolerance up to 5 years after an index pregnancy complicated by gestational diabetes defined using International Association of Diabetes and Pregnancy Study Groups criteria (Ph.D. Thesis)*. Department of Medicine, National University of Ireland Galway; 2015.

53. Catalano PM, Hauguel-De Mouzon S. Is it time to revisit the Pedersen hypothesis in the face of the obesity epidemic? *Am J Obstet Gynecol.* 2011;204(6):479-487.

54. Pedersen J. The pregnant diabetic and her newborn: Problems and management. In. Baltimore MD: William & Wilkins; 1967:128-137.
55. Pedersen J. *Diabetes and pregnancy:Blood sugar of newborn infants (Ph.D. Thesis).* Copenhagen, Danish Science Press; 1952.
56. Inkster ME, Fahey TP, Donnan PT, Leese GP, Mires GJ, Murphy DJ. Poor glycated haemoglobin control and adverse pregnancy outcomes in type 1 and type 2 diabetes mellitus: systematic review of observational studies. *BMC Pregnancy Childbirth.* 2006;6:30.
57. Macintosh MC, Fleming KM, Bailey JA, et al. Perinatal mortality and congenital anomalies in babies of women with type 1 or type 2 diabetes in England, Wales, and Northern Ireland: population based study. *BMJ.* 2006;333(7560):177.
58. Dunne FP, Avalos G, Durkan M, et al. ATLANTIC DIP: pregnancy outcome for women with pregestational diabetes along the Irish Atlantic seaboard. *Diabetes Care.* 2009;32(7):1205-1206.
59. Klein BE, Moss SE, Klein R. Effect of pregnancy on progression of diabetic retinopathy. *Diabetes Care.* 1990;13(1):34-40.
60. Rasmussen KL, Laugesen CS, Ringholm L, Vestgaard M, Damm P, Mathiesen ER. Progression of diabetic retinopathy during pregnancy in women with type 2 diabetes. *Diabetologia.* 2010;53(6):1076-1083.
61. Kaaja R, Loukovaara S. Progression of retinopathy in type 1 diabetic women during pregnancy. *Curr Diabetes Rev.* 2007;3(2):85-93.
62. Ringholm L, Damm JA, Vestgaard M, Damm P, Mathiesen ER. Diabetic Nephropathy in Women With Preexisting Diabetes: From Pregnancy Planning to Breastfeeding. *Curr Diab Rep.* 2016;16(2):12.
63. Healthcare Quality Improvement Partnership. *National Pregnancy in Diabetes Audit*. 2015. http://www.hqip.org.uk/resources/national-pregnancy-in-diabetes-audit-report-2015/ Accessed January 23rd 2016.
64. Law GR, Ellison GT, Secher AL, et al. Analysis of Continuous Glucose Monitoring in Pregnant Women With Diabetes: Distinct

Temporal Patterns of Glucose Associated With Large-for-Gestational-Age Infants. *Diabetes Care.* 2015.

65. Confidential Enquiry into Maternal and Child Health. *Diabetes in Pregnancy: Are we providing the best care? Findings of a National Enquiry: England, Wales and Northern Ireland.* CEMACH: London 2007.
66. Evers IM, de Valk HW, Mol BW, ter Braak EW, Visser GH. Macrosomia despite good glycaemic control in Type I diabetic pregnancy; results of a nationwide study in The Netherlands. *Diabetologia.* 2002;45(11):1484-1489.
67. Murphy HR, Roland JM, Skinner TC, et al. Effectiveness of a Regional Prepregnancy Care Program in Women With Type 1 and Type 2 Diabetes Benefits beyond glycemic control. *Diabetes Care.* 2010;33(12):2514-2520.
68. Bytoft B, Knorr S, Vlachova Z, et al. Long-term Cognitive Implications of Intrauterine Hyperglycemia in Adolescent Offspring of Women With Type 1 Diabetes (the EPICOM Study). *Diabetes Care.* 2016;39(8):1356-1363.
69. Dabelea D, Knowler WC, Pettitt DJ. Effect of diabetes in pregnancy on offspring: follow-up research in the Pima Indians. *J Matern Fetal Med.* 2000;9(1):83-88.
70. Diabetes care and research in Europe: the Saint Vincent declaration. *Diabet Med.* 1990;7(4):360.
71. Owens LA, Avalos G, Kirwan B, Carmody L, Dunne F. ATLANTIC DIP: Closing the Loop A change in clinical practice can improve outcomes for women with pregestational diabetes. *Diabetes Care.* 2012;35(8):1669-1671.
72. Temple R, Aldridge V, Greenwood R, Heyburn P, Sampson M, Stanley K. Association between outcome of pregnancy and glycaemic control in early pregnancy in type 1 diabetes: population based study. *BMJ.* 2002;325(7375):1275-1276.
73. Steel JM, Johnstone FD, Smith AF, Duncan LJ. Five years' experience of a "prepregnancy" clinic for insulin-dependent diabetics. *Br Med J (Clin Res Ed).* 1982;285(6338):353-356.

74. Mathiesen ER, Kinsley B, Amiel SA, et al. Maternal glycemic control and hypoglycemia in type 1 diabetic pregnancy: a randomized trial of insulin aspart versus human insulin in 322 pregnant women. *Diabetes Care.* 2007;30(4):771-776.
75. Garg SK, Frias JP, Anil S, Gottlieb PA, MacKenzie T, Jackson WE. Insulin lispro therapy in pregnancies complicated by type 1 diabetes: glycemic control and maternal and fetal outcomes. *Endocr Pract.* 2003;9(3):187-193.
76. Mathiesen ER, Hod M, Ivanisevic M, et al. Maternal efficacy and safety outcomes in a randomized, controlled trial comparing insulin detemir with NPH insulin in 310 pregnant women with type 1 diabetes. *Diabetes Care.* 2012;35(10):2012-2017.
77. Suffecool K, Rosenn B, Niederkofler EE, et al. Insulin detemir does not cross the human placenta. *Diabetes Care.* 2015;38(2):e20-21.
78. Hod M, Mathiesen ER, Jovanovič L, et al. A randomized trial comparing perinatal outcomes using insulin detemir or neutral protamine Hagedorn in type 1 diabetes. *J Matern Fetal Neonatal Med.* 2014;27(1):7-13.
79. Di Cianni G, Torlone E, Lencioni C, et al. Perinatal outcomes associated with the use of glargine during pregnancy. *Diabet Med.* 2008;25(8):993-996.
80. Gallen IW, Jaap A, Roland JM, Chirayath HH. Survey of glargine use in 115 pregnant women with Type 1 diabetes. *Diabet Med.* 2008;25(2):165-169.
81. Wahabi HA, Alzeidan RA, Esmaeil SA. Pre-pregnancy care for women with pre-gestational diabetes mellitus: a systematic review and meta-analysis. *Bmc Public Health.* 2012;12.
82. Murphy HR, Temple RC, Ball VE, et al. Personal experiences of women with diabetes who do not attend pre-pregnancy care. *Diabetic Medicine.* 2010;27(1):92-100.
83. O'Higgins S, McGuire BE, Mustafa E, Dunne F. Barriers and facilitators to attending pre-pregnancy care services: the ATLANTIC-DIP experience. *Diabetic Medicine.* 2014;31(3):366-374.

84. Hadden DR. The management of diabetes in pregnancy. *Postgrad Med J.* 1996;72(851):525-531.
85. Maresh MJA, Holmes VA, Patterson CC, et al. Glycemic Targets in the Second and Third Trimester of Pregnancy for Women With Type 1 Diabetes. *Diabetes Care.* 2015;38(1):34-42.
86. Egan AM, Dennedy MC, Al-Ramli W, Heerey A, Avalos G, Dunne F. ATLANTIC-DIP: excessive gestational weight gain and pregnancy outcomes in women with gestational or pregestational diabetes mellitus. *J Clin Endocrinol Metab.* 2014;99(1):212-219.
87. Institute of Medicine (US) and National Research Council (US) Committee to Reexamine IOM Pregnancy Weight Guidelines. In: Rasmussen KM, Yaktine AL, ed. *Weight Gain During Pregnancy: Reexamining the Guidelines.* Washington, DC: National Acadamies Press (US); 2009.
88. Castorino K, Jovanovič L. Pregnancy and diabetes management: advances and controversies. *Clin Chem.* 2011;57(2):221-230.
89. Vestgaard M, Ringholm L, Laugesen CS, Rasmussen KL, Damm P, Mathiesen ER. Pregnancy-induced sight-threatening diabetic retinopathy in women with Type 1 diabetes. *Diabet Med.* 2010;27(4):431-435.
90. Nielsen LR, Damm P, Mathiesen ER. Improved pregnancy outcome in type 1 diabetic women with microalbuminuria or diabetic nephropathy: effect of intensified antihypertensive therapy? *Diabetes Care.* 2009;32(1):38-44.
91. Feldberg D, Dicker D, Samuel N, Peleg D, Karp M, Goldman JA. Intrapartum management of insulin-dependent diabetes mellitus (IDDM) gestants. A comparative study of constant intravenous insulin infusion and continuous subcutaneous insulin infusion pump (CSIIP). *Acta Obstet Gynecol Scand.* 1988;67(4):333-338.
92. Balsells M, Corcoy R, Adelantado JM, García-Patterson A, Altirriba O, de Leiva A. Gestational diabetes mellitus: metabolic control during labour. *Diabetes Nutr Metab.* 2000;13(5):257-262.
93. Dixon KC, Ferris RL, Marikar D, et al. Definition and monitoring of neonatal hypoglycaemia: a nationwide survey of NHS England

Neonatal Units. *Arch Dis Child Fetal Neonatal Ed.* 2017;102(1):F92-F93.

94. Riviello C, Mello G, Jovanovic LG. Breastfeeding and the basal insulin requirement in type 1 diabetic women. *Endocr Pract.* 2009;15(3):187-193.
95. Howie PW, Forsyth JS, Ogston SA, Clark A, Florey CD. Protective effect of breast feeding against infection. *BMJ.* 1990;300(6716):11-16.
96. Mayer-Davis EJ, Rifas-Shiman SL, Zhou L, Hu FB, Colditz GA, Gillman MW. Breast-feeding and risk for childhood obesity: does maternal diabetes or obesity status matter? *Diabetes Care.* 2006;29(10):2231-2237.
97. von Kries R, Koletzko B, Sauerwald T, et al. Breast feeding and obesity: cross sectional study. *BMJ.* 1999;319(7203):147-150.
98. Glueck CJ, Wang P. Metformin before and during pregnancy and lactation in polycystic ovary syndrome. *Expert Opin Drug Saf.* 2007;6(2):191-198.
99. Finkelstein SA, Keely E, Feig DS, Tu X, Yasseen AS, Walker M. Breastfeeding in women with diabetes: lower rates despite greater rewards. A population-based study. *Diabet Med.* 2013;30(9):1094-1101.
100. Bech K, Høier-Madsen M, Feldt-Rasmussen U, Jensen BM, Mølsted-Pedersen L, Kühl C. Thyroid function and autoimmune manifestations in insulin-dependent diabetes mellitus during and after pregnancy. *Acta Endocrinol (Copenh).* 1991;124(5):534-539.
101. Egan AM, Danyliv A, Carmody L, Kirwan B, Dunne FP. A Prepregnancy Care Program for Women With Diabetes: Effective and Cost Saving. *J Clin Endocrinol Metab.* 2016;101(4):1807-1815.
102. Hicom Homepage. http://www.hicom.co.uk. Accessed January 23rd 2017.
103. Wahabi HA, Alzeidan RA, Bawazeer GA, Alansari LA, Esmaeil SA. Preconception care for diabetic women for improving maternal and fetal outcomes: a systematic review and meta-analysis. *Bmc Pregnancy and Childbirth.* 2010;10.

104. Kitzmiller JL, Gavin LA, Gin GD, Jovanovic-Peterson L, Main EK, Zigrang WD. Preconception care of diabetes. Glycemic control prevents congenital anomalies. *JAMA.* 1991;265(6):731-736.
105. Rosenn B, Miodovnik M, Combs CA, Khoury J, Siddiqi TA. Pre-conception management of insulin-dependent diabetes: improvement of pregnancy outcome. *Obstet Gynecol.* 1991;77(6):846-849.
106. Fuhrmann K, Reiher H, Semmler K, Fischer F, Fischer M, Glöckner E. Prevention of congenital malformations in infants of insulin-dependent diabetic mothers. *Diabetes Care.* 1983;6(3):219-223.
107. Willhoite MB, Bennert HW, Palomaki GE, et al. The impact of preconception counseling on pregnancy outcomes. The experience of the Maine Diabetes in Pregnancy Program. *Diabetes Care.* 1993;16(2):450-455.
108. Steel JM, Johnstone FD, Hepburn DA, Smith AF. Can prepregnancy care of diabetic women reduce the risk of abnormal babies? *BMJ.* 1990;301(6760):1070-1074.
109. Temple RC, Aldridge VJ, Murphy HR. Prepregnancy care and pregnancy outcomes in women with type 1 diabetes. *Diabetes Care.* 2006;29(8):1744-1749.
110. Correa A, Botto L, Liu Y, Mulinare J, Erickson JD. Do multivitamin supplements attenuate the risk for diabetes-associated birth defects? *Pediatrics.* 2003;111(5 Pt 2):1146-1151.
111. Correa A, Gilboa SM, Botto LD, et al. Lack of periconceptional vitamins or supplements that contain folic acid and diabetes mellitus-associated birth defects. *Am J Obstet Gynecol.* 2012;206(3):218.e211-213.
112. Pregnancy outcomes in the Diabetes Control and Complications Trial. *Am J Obstet Gynecol.* 1996;174(4):1343-1353.
113. Evers IM, de Valk HW, Visser GH. Risk of complications of pregnancy in women with type 1 diabetes: nationwide prospective study in the Netherlands. *BMJ.* 2004;328(7445):915.
114. Persson M, Norman M, Hanson U. Obstetric and perinatal outcomes in type 1 diabetic pregnancies: A large, population-based study. *Diabetes Care.* 2009;32(11):2005-2009.

115. Jensen DM, Korsholm L, Ovesen P, et al. Peri-conceptional A1C and risk of serious adverse pregnancy outcome in 933 women with type 1 diabetes. *Diabetes Care.* 2009;32(6):1046-1048.
116. Middleton P, Crowther CA, Simmonds L. Different intensities of glycaemic control for pregnant women with pre-existing diabetes. *Cochrane Database Syst Rev.* 2016(5):CD008540.
117. Jovanovic L, Druzin M, Peterson CM. Effect of euglycemia on the outcome of pregnancy in insulin-dependent diabetic women as compared with normal control subjects. *Am J Med.* 1981;71(6):921-927.
118. Jensen DM, Damm P, Moelsted-Pedersen L, et al. Outcomes in type 1 diabetic pregnancies: a nationwide, population-based study. *Diabetes Care.* 2004;27(12):2819-2823.
119. Atlantic Diabetes in Pregnancy. *Guidelines for the Management of Diabetes in Pregnancy.* 2015; http://atlanticdipireland.com/professionals/guidelines/guidelines-atlantic-dip-clinical-guidelines-for-the-management-of-diabetes-in-pregnancy/. Accessed January 23rd 2017.
120. Atlantic Diabetes in Pregnancy. Information booklet for mothers with diabetes. http://atlanticdipireland.com/professionals/guidelines/guidelines-atlantic-dip-information-booklet-for-mothers-with-diabetes/. Accessed January 23rd 2017.
121. Atlantic Diabetes in Pregnancy Homepage. http://atlanticdipireland.com. Accessed January 23rd 2017.
122. Child Growth Foundation. *BMI Charts. UK cross-sectional reference data: 1990/1*. London: Child Growth Foundation; 1997.
123. European Surveillance of Congenital Anomalies (EUROCAT). *EUROCAT Guide 1.3 and reference documents. Instructions for the registration and surveillance of congenital anomalies.* 2005; http://www.eurocat-network.eu/content/EUROCAT-Guide-1.3.pdf. Accessed January 14th, 2017.
124. Tennant PW, Glinianaia SV, Bilous RW, Rankin J, Bell R. Pre-existing diabetes, maternal glycated haemoglobin, and the risks of

fetal and infant death: a population-based study. *Diabetologia.* 2014;57(2):285-294.

125. Jovanovic L, Peterson CM. Insulin and glucose requirements during the first stage of labor in insulin-dependent diabetic women. *Am J Med.* 1983;75(4):607-612.
126. Stewart ZA, Wilinska ME, Hartnell S, et al. Closed-Loop Insulin Delivery during Pregnancy in Women with Type 1 Diabetes. *N Engl J Med.* 2016;375(7):644-654.
127. Feig DS, Murphy K, Asztalos E, et al. Metformin in women with type 2 diabetes in pregnancy (MiTy): a multi-center randomized controlled trial. *BMC Pregnancy Childbirth.* 2016;16(1):173.
128. Coetzee EJ, Jackson WP. Metformin in management of pregnant insulin-independent diabetics. *Diabetologia.* 1979;16(4):241-245.
129. Gutzin SJ, Kozer E, Magee LA, Feig DS, Koren G. The safety of oral hypoglycemic agents in the first trimester of pregnancy: a meta-analysis. *Can J Clin Pharmacol.* 2003;10(4):179-183.
130. Gilbert C, Valois M, Koren G. Pregnancy outcome after first-trimester exposure to metformin: a meta-analysis. *Fertil Steril.* 2006;86(3):658-663.
131. Dennedy MC, Avalos G, O'Reilly MW, O'Sullivan EP, Gaffney G, Dunne F. ATLANTIC-DIP: raised maternal body mass index (BMI) adversely affects maternal and fetal outcomes in glucose-tolerant women according to International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria. *J Clin Endocrinol Metab.* 2012;97(4):E608-612.
132. Scifres CM, Feghali MN, Althouse AD, Caritis SN, Catov JM. Effect of excess gestational weight gain on pregnancy outcomes in women with type 1 diabetes. *Obstet Gynecol.* 2014;123(6):1295-1302.
133. Ehrenberg HM, Durnwald CP, Catalano P, Mercer BM. The influence of obesity and diabetes on the risk of cesarean delivery. *Am J Obstet Gynecol.* 2004;191(3):969-974.

134. Takoudes TC, Weitzen S, Slocum J, Malee M. Risk of cesarean wound complications in diabetic gestations. *Am J Obstet Gynecol.* 2004;191(3):958-963.

135. Owens LA, Egan AM, Carmody L, Dunne F. Ten years of optimizing outcomes for women with type 1 and type 2 diabetes in pregnancy - the Atlantic DIP experience. *J Clin Endocrinol Metab.* 2016:jc20153817.

136. Chu SY, Callaghan WM, Bish CL, D'Angelo D. Gestational weight gain by body mass index among US women delivering live births, 2004-2005: fueling future obesity. *Am J Obstet Gynecol.* 2009;200(3):271.e271-277.

137. Mamun AA, O'Callaghan M, Callaway L, Williams G, Najman J, Lawlor DA. Associations of gestational weight gain with offspring body mass index and blood pressure at 21 years of age: evidence from a birth cohort study. *Circulation.* 2009;119(13):1720-1727.

138. Nohr EA, Vaeth M, Baker JL, Sørensen TIa, Olsen J, Rasmussen KM. Combined associations of prepregnancy body mass index and gestational weight gain with the outcome of pregnancy. *Am J Clin Nutr.* 2008;87(6):1750-1759.

139. Yee LM, Cheng YW, Inturrisi M, Caughey AB. Effect of gestational weight gain on perinatal outcomes in women with type 2 diabetes mellitus using the 2009 Institute of Medicine guidelines. *Am J Obstet Gynecol.* 2011;205(3):257.e251-256.

140. Black MH, Sacks DA, Xiang AH, Lawrence JM. The relative contribution of prepregnancy overweight and obesity, gestational weight gain, and IADPSG-defined gestational diabetes mellitus to fetal overgrowth. *Diabetes Care.* 2013;36(1):56-62.

141. Owens LA, O'Sullivan EP, Kirwan B, et al. ATLANTIC DIP: the impact of obesity on pregnancy outcome in glucose-tolerant women. *Diabetes Care.* 2010;33(3):577-579.

142. Mamun AA, Callaway LK, O'Callaghan MJ, et al. Associations of maternal pre-pregnancy obesity and excess pregnancy weight gains with adverse pregnancy outcomes and length of hospital stay. *BMC Pregnancy Childbirth.* 2011;11:62.

143. Ludwig DS, Currie J. The association between pregnancy weight gain and birthweight: a within-family comparison. *Lancet.* 2010;376(9745):984-990.
144. Henriksen T. The macrosomic fetus: a challenge in current obstetrics. *Acta Obstet Gynecol Scand.* 2008;87(2):134-145.
145. Koyanagi A, Zhang J, Dagvadorj A, et al. Macrosomia in 23 developing countries: an analysis of a multicountry, facility-based, cross-sectional survey. *Lancet.* 2013;381(9865):476-483.
146. Dennedy MC, Dunne F. The maternal and fetal impacts of obesity and gestational diabetes on pregnancy outcome. *Best Pract Res Clin Endocrinol Metab.* 2010;24(4):573-589.
147. Oostdam N, van Poppel MN, Wouters MG, et al. No effect of the FitFor2 exercise programme on blood glucose, insulin sensitivity, and birthweight in pregnant women who were overweight and at risk for gestational diabetes: results of a randomised controlled trial. *BJOG.* 2012;119(9):1098-1107.
148. Kinnunen TI, Raitanen J, Aittasalo M, Luoto R. Preventing excessive gestational weight gain--a secondary analysis of a cluster-randomised controlled trial. *Eur J Clin Nutr.* 2012;66(12):1344-1350.
149. Thangaratinam S, Rogozinska E, Jolly K, et al. Effects of interventions in pregnancy on maternal weight and obstetric outcomes: meta-analysis of randomised evidence. *BMJ.* 2012;344:e2088.
150. Oteng-Ntim E, Varma R, Croker H, Poston L, Doyle P. Lifestyle interventions for overweight and obese pregnant women to improve pregnancy outcome: systematic review and meta-analysis. *BMC Med.* 2012;10:47.
151. Pollex EK, Feig DS, Lubetsky A, Yip PM, Koren G. Insulin glargine safety in pregnancy: a transplacental transfer study. *Diabetes Care.* 2010;33(1):29-33.
152. Di Mario U, Fallucca F, Gargiulo P, et al. Insulin-anti-insulin complexes in diabetic women and their neonates. *Diabetologia.* 1984;27 Suppl:83-86.

153. Desoye G, Hofmann HH, Weiss PA. Insulin binding to trophoblast plasma membranes and placental glycogen content in well-controlled gestational diabetic women treated with diet or insulin, in well-controlled overt diabetic patients and in healthy control subjects. *Diabetologia.* 1992;35(1):45-55.

154. Hiden U, Maier A, Bilban M, et al. Insulin control of placental gene expression shifts from mother to foetus over the course of pregnancy. *Diabetologia.* 2006;49(1):123-131.

155. Rowan JA, Hague WM, Gao W, Battin MR, Moore MP, Investigators MT. Metformin versus insulin for the treatment of gestational diabetes. *N Engl J Med.* 2008;358(19):2003-2015.

156. Charles B, Norris R, Xiao X, Hague W. Population pharmacokinetics of metformin in late pregnancy. *Ther Drug Monit.* 2006;28(1):67-72.

157. Barrett HL, Dekker Nitert M, Jones L, et al. Determinants of maternal triglycerides in women with gestational diabetes mellitus in the Metformin in Gestational Diabetes (MiG) study. *Diabetes Care.* 2013;36(7):1941-1946.

158. Rowan JA, Rush EC, Obolonkin V, Battin M, Wouldes T, Hague WM. Metformin in gestational diabetes: the offspring follow-up (MiG TOFU): body composition at 2 years of age. *Diabetes Care.* 2011;34(10):2279-2284.

159. Carlsen SM, Martinussen MP, Vanky E. Metformin's effect on first-year weight gain: a follow-up study. *Pediatrics.* 2012;130(5):e1222-1226.

160. Chiswick C, Reynolds RM, Denison F, et al. Effect of metformin on maternal and fetal outcomes in obese pregnant women (EMPOWaR): a randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol.* 2015;3(10):778-786.

161. Dunne F. A Clinical Trial of the Effectiveness of Metformin in Addition to Usual Care in the Reduction of Gestational Diabetes Mellitus (EMERGE). 2016; https://clinicaltrials.gov/ct2/show/NCT02980276. Accessed January 13th 2017.

162. Fattah C, Farah N, Barry SC, O'Connor N, Stuart B, Turner MJ. Maternal weight and body composition in the first trimester of pregnancy. *Acta Obstet Gynecol Scand.* 2010;89(7):952-955.

163. Hampshire R, Wharton H, Leigh R, Wright A, Dodson P. Screening for diabetic retinopathy in pregnancy using photographic review clinics. *Diabet Med.* 2013;30(4):475-477.

164. Chew EY, Mills JL, Metzger BE, et al. Metabolic control and progression of retinopathy. The Diabetes in Early Pregnancy Study. National Institute of Child Health and Human Development Diabetes in Early Pregnancy Study. *Diabetes Care.* 1995;18(5):631-637.

165. Lövestam-Adrian M, Agardh CD, Aberg A, Agardh E. Pre-eclampsia is a potent risk factor for deterioration of retinopathy during pregnancy in Type 1 diabetic patients. *Diabet Med.* 1997;14(12):1059-1065.

166. Dibble CM, Kochenour NK, Worley RJ, Tyler FH, Swartz M. Effect of pregnancy on diabetic retinopathy. *Obstet Gynecol.* 1982;59(6):699-704.

167. Price JH, Hadden DR, Archer DB, Harley JM. Diabetic retinopathy in pregnancy. *Br J Obstet Gynaecol.* 1984;91(1):11-17.

168. UK National Screening Committee. *Essential Elements in developing a Diabetic Retinopathy Screening Programme. Workbook 4.3.* 2009. http://rcophth-website.www.premierithosting.com/docs/publications/published-guidelines/ENSPDR_Workbook_2009.pdf. Accessed January 13th 2017.

169. The Diabetes Control and Complications Trial Research Group. Effect of pregnancy on microvascular complications in the diabetes control and complications trial. *Diabetes Care.* 2000;23(8):1084-1091.

170. Temple RC, Aldridge VA, Sampson MJ, Greenwood RH, Heyburn PJ, Glenn A. Impact of pregnancy on the progression of diabetic retinopathy in Type 1 diabetes. *Diabet Med.* 2001;18(7):573-577.

171. Arun CS, Taylor R. Influence of pregnancy on long-term progression of retinopathy in patients with type 1 diabetes. *Diabetologia.* 2008;51(6):1041-1045.
172. Hemachandra A, Ellis D, Lloyd CE, Orchard TJ. The influence of pregnancy on IDDM complications. *Diabetes Care.* 1995;18(7):950-954.
173. Early worsening of diabetic retinopathy in the Diabetes Control and Complications Trial. *Arch Ophthalmol.* 1998;116(7):874-886.
174. Rosenn B, Miodovnik M, Kranias G, et al. Progression of diabetic retinopathy in pregnancy: association with hypertension in pregnancy. *Am J Obstet Gynecol.* 1992;166(4):1214-1218.
175. Axer-Siegel R, Hod M, Fink-Cohen S, et al. Diabetic retinopathy during pregnancy. *Ophthalmology.* 1996;103(11):1815-1819.
176. Hellstedt T, Kaaja R, Teramo K, Immonen I. The effect of pregnancy on mild diabetic retinopathy. *Graefes Arch Clin Exp Ophthalmol.* 1997;235(7):437-441.
177. Bell R, Glinianaia SV, Tennant PWG, Bilous RW, Rankin J. Peri-conception hyperglycaemia and nephropathy are associated with risk of congenital anomaly in women with pre-existing diabetes: a population-based cohort study. *Diabetologia.* 2012;55(4):936-947.
178. Tennant PW, Bilous RW, Prathapan S, Bell R. Risk and recurrence of serious adverse outcomes in the first and second pregnancies of women with preexisting diabetes. *Diabetes Care.* 2015;38(4):610-619.
179. Mistry H, Heazell AE, Vincent O, Roberts T. A structured review and exploration of the healthcare costs associated with stillbirth and a subsequent pregnancy in England and Wales. *BMC Pregnancy Childbirth.* 2013;13:236.
180. Pourat N, Martinez A, Jones J, Gregory K, Korst L, Kominski G. *Costs of Gestational Hypertensive Disorders in California: Hypertension, Preeclampsia and Eclampsia.* 2013. UCLA Center for Health Policy Research, Los Angeles. http://healthpolicy.ucla.edu/publications/Documents/PDF/gestationaldisordersreport-oct2013.pdf. Accessed January 14th 2017.

181. Shmueli A, Meiri H, Gonen R. Economic assessment of screening for pre-eclampsia. *Prenat Diagn.* 2012;32(1):29-38.
182. The Organisation for Economic Co-operation and Development (OECD). *PPPs and exchange rates.* 2014; http://stats.oecd.org/Index.aspx?datasetcode=SNA_TABLE4. Accessed January 14th 2017.
183. National Casemix Programme. *Ready Reckoner of Acute Hospital Inpatient and Daycase Activity and Costs.* Ireland: Health Service Executive. 2014
184. Central Statistics Office (CSO) Ireland. Consumer Price Index by Commodity Group and Year. 2014. http://www.cso.ie/. Accessed January 14th 2017.
185. Carmody L, Egan AM, Dunne FP. Postpartum glucose testing for women with gestational diabetes mellitus: Improving regional recall rates. *Diabetes Res Clin Pract.* 2015.
186. Wellings K, Jones KG, Mercer CH, et al. The prevalence of unplanned pregnancy and associated factors in Britain: findings from the third National Survey of Sexual Attitudes and Lifestyles (Natsal-3). *Lancet.* 2013;382(9907):1807-1816.
187. Mount Sinai Hospital C. Continuous Glucose Monitoring in Women with Type 1 diabetes in Pregnancy Trial. https://clinicaltrials.gov/ct2/results?term=conceptt&Search=Search. Accessed January 14th 2017.
188. Secher AL, Parellada CB, Ringholm L, Asbjörnsdóttir B, Damm P, Mathiesen ER. Higher gestational weight gain is associated with increasing offspring birth weight independent of maternal glycemic control in women with type 1 diabetes. *Diabetes Care.* 2014;37(10):2677-2684.
189. Influence of intensive diabetes treatment on body weight and composition of adults with type 1 diabetes in the Diabetes Control and Complications Trial. *Diabetes Care.* 2001;24(10):1711-1721.

190. Elixhauser A, Weschler JM, Kitzmiller JL, et al. Cost-benefit analysis of preconception care for women with established diabetes mellitus. *Diabetes Care.* 1993;16(8):1146-1157.
191. Peterson C, Grosse SD, Li R, et al. Preventable health and cost burden of adverse birth outcomes associated with pregestational diabetes in the United States. *Am J Obstet Gynecol.* 2015;212(1):74.e71-79.
192. Boggess KA, Berggren EK. Preconception care has the potential for a high return on investment. *Am J Obstet Gynecol.* 2015;212(1):1-3.
193. Egan AM, Murphy HR, Dunne FP. The management of type 1 and type 2 diabetes in pregnancy. *QJM.* 2015;108(12):923-927.
194. Penney GC, Mair G, Pearson DWM. Outcomes of pregnancies in women with type I diabetes in Scotland: a national population-based study. *Bjog-an International Journal of Obstetrics and Gynaecology.* 2003;110(3):315-318.
195. Harman NL, Bruce IA, Callery P, et al. MOMENT--Management of Otitis Media with Effusion in Cleft Palate: protocol for a systematic review of the literature and identification of a core outcome set using a Delphi survey. *Trials.* 2013;14:70.
196. Williamson PR, Altman DG, Blazeby JM, et al. Developing core outcome sets for clinical trials: issues to consider. *Trials.* 2012;13:132.
197. Saini P, Loke YK, Gamble C, Altman DG, Williamson PR, Kirkham JJ. Selective reporting bias of harm outcomes within studies: findings from a cohort of systematic reviews. *BMJ.* 2014;349:g6501.
198. Smith V, Clarke M, Williamson P, Gargon E. Survey of new 2007 and 2011 Cochrane reviews found 37% of prespecified outcomes not reported. *J Clin Epidemiol.* 2015;68(3):237-245.
199. Tieu J, Middleton P, Crowther CA. Preconception care for diabetic women for improving maternal and infant health. *Cochrane Database of Systematic Reviews.* 2010(12).
200. Charron-Prochownik D, Ferons-Hannan M, Sereika S, Becker D. Randomized efficacy trial of early preconception counseling for

diabetic teens (READY-Girls). *Diabetes Care.* 2008;31(7):1327-1330.

201. Gargon E, Williamson PR, Altman DG, Blazeby JM, Clarke M. The COMET Initiative database: progress and activities from 2011 to 2013. *Trials.* 2014;15:279.
202. Khan KS, Romero R, Initiative CEoJpiC. The CROWN initiative: journal editors invite researchers to develop core outcomes in women's health. *Am J Obstet Gynecol.* 2014;211(6):575-576.
203. Devane D, Begley CM, Clarke M, Horey D, OBoyle C. Evaluating maternity care: a core set of outcome measures. *Birth.* 2007;34(2):164-172.
204. Chen RC, Chang P, Vetter RJ, et al. Recommended patient-reported core set of symptoms to measure in prostate cancer treatment trials. *J Natl Cancer Inst.* 2014;106(7).
205. Sibley KM, Howe T, Lamb SE, et al. Recommendations for a core outcome set for measuring standing balance in adult populations: a consensus-based approach. *PLoS One.* 2015;10(3):e0120568.
206. Sinha A, Rajan M, Hoerger T, Pogach L. Costs and Consequences Associated With Newer Medications for Glycemic Control in Type 2 Diabetes. *Diabetes Care.* 2010;33(4):695-700.
207. MacLennan S, Bekema HJ, Williamson PR, et al. A core outcome set for localised prostate cancer effectiveness trials: protocol for a systematic review of the literature and stakeholder involvement through interviews and a Delphi survey. *Trials.* 2015;16:76.
208. Egan AM, Smith V, Devane D, Dunne FP. Effectiveness of prepregnancy care for women with pregestational diabetes mellitus: protocol for a systematic review of the literature and identification of a core outcomes set using a Delphi survey. *Trials.* 2015;16.
209. Kirkham JJ, Gorst S, Altman DG, et al. Core Outcome Set-STAndards for Reporting: The COS-STAR Statement. *PLoS Med.* 2016;13(10):e1002148.
210. Core Outcome Measures in Effectiveness Trials (COMET) Initiaitive Database. http://www.comet-initiative.org. Accessed 3rd November 2016.

211. Callec R, Perdriolle-Galet E, Sery GA, Morel O. Type 2 diabetes in pregnancy: Rates of fetal malformations and level of preconception care. *Journal of Obstetrics and Gynaecology.* 2014;34(7):648-649.
212. Neff KJ, Forde R, Gavin C, et al. Pre-pregnancy care and pregnancy outcomes in type 1 diabetes mellitus: a comparison of continuous subcutaneous insulin infusion and multiple daily injection therapy. *Irish Journal of Medical Science.* 2014;183(3):397-403.
213. Tripathi A, Rankin J, Aarvold J, Chandler C, Bell R. Preconception Counseling in Women With Diabetes A population-based study in the North of England. *Diabetes Care.* 2010;33(3):586-588.
214. Temple RC, Aldridge V, Stanley K, Murphy HR. Glycaemic control throughout pregnancy and risk of pre-eclampsia in women with type I diabetes. *Bjog-an International Journal of Obstetrics and Gynaecology.* 2006;113(11):1329-1332.
215. Boulot P, Chabbert-Buffet N, d'Ercole C, et al. French multicentric survey of outcome of pregnancy in women with pregestational diabetes. *Diabetes Care.* 2003;26(11):2990-2993.
216. Glinianaia SV, Tennant PWG, Crowder D, Nayar R, Bell R. Fifteen-year trends and predictors of preparation for pregnancy in women with pre-conception Type 1 and Type 2 diabetes: a population-based cohort study. *Diabetic Medicine.* 2014;31(9):1104-1113.
217. Wong VW, Suwandarathne H, Russell H. Women with pre-existing diabetes under the care of diabetes specialist prior to pregnancy: are their outcomes better? *Australian & New Zealand Journal of Obstetrics & Gynaecology.* 2013;53(2):207-210.
218. Dunne FP, Brydon P, Smith T, Essex M, Nicholson H, Dunn J. Pre-conception diabetes care in insulin-dependent diabetes mellitus. *QJM.* 1999;92(3):175-176.
219. Glinianaia SV, Tennant PWG, Bilous RW, Rankin J, Bell R. HbA(1c) and birthweight in women with pre-conception type 1 and type 2 diabetes: a population-based cohort study. *Diabetologia.* 2012;55(12):3193-3203.
220. McElvy SS, Miodovnik M, Rosenn B, et al. A focused preconceptional and early pregnancy program in women with type 1

diabetes reduces perinatal mortality and malformation rates to general population levels. *J Matern Fetal Med.* 2000;9(1):14-20.

221. Kekäläinen P, Juuti M, Walle T, Laatikainen T. Pregnancy planning in type 1 diabetic women improves glycemic control and pregnancy outcomes. *J Matern Fetal Neonatal Med.* 2016;29(14):2252-2258.
222. Kallas-Koeman M, Khandwala F, Donovan LE. Rate of Preconception Care in Women with Type 2 Diabetes Still Lags behind that of Women with Type 1 Diabetes. *Canadian Journal of Diabetes.* 2012;36(4):170-174.
223. Herman WH, Janz NK, Becker MP, Charron-Prochownik D. Diabetes and pregnancy - Preconception care, pregnancy outcomes, resource utilization and costs. *Journal of Reproductive Medicine.* 1999;44(1):33-38.
224. Rowe BR, Rowbotham CJ, Barnett AH. Pre-conception counselling, birth weight, and congenital abnormalities in established and gestational diabetic pregnancy. *Diabetes Res.* 1987;6(1):33-35.
225. Jensen BM, Kühl C, Mølsted-Pedersen L, Saurbrey N, Fog-Pedersen J. Preconceptional treatment with insulin infusion pumps in insulin-dependent diabetic women with particular reference to prevention of congenital malformations. *Acta Endocrinol Suppl (Copenh).* 1986;277:81-85.
226. Galindo A, Burguillo AG, Azriel S, Fuente PeL. Outcome of fetuses in women with pregestational diabetes mellitus. *J Perinat Med.* 2006;34(4):323-331.
227. Damm P, Mølsted-Pedersen L. Significant decrease in congenital malformations in newborn infants of an unselected population of diabetic women. *Am J Obstet Gynecol.* 1989;161(5):1163-1167.
228. Goldman JA, Dicker D, Feldberg D, Yeshaya A, Samuel N, Karp M. Pregnancy outcome in patients with insulin-dependent diabetes mellitus with preconceptional diabetic control: a comparative study. *Am J Obstet Gynecol.* 1986;155(2):293-297.
229. Fuhrmann K. Treatment of pregnant insulin-dependent diabetic women. *Acta Endocrinol Suppl (Copenh).* 1986;277:74-76.

230. Fuhrmann K, Reiher H, Semmler K, Glöckner E. The effect of intensified conventional insulin therapy before and during pregnancy on the malformation rate in offspring of diabetic mothers. *Exp Clin Endocrinol.* 1984;83(2):173-177.

231. García-Patterson A, Corcoy R, Rigla M, et al. Does preconceptional counselling in diabetic women influence perinatal outcome? *Ann Ist Super Sanita.* 1997;33(3):333-336.

232. Feig DS, Corcoy R, Jensen DM, et al. Diabetes in pregnancy outcomes: a systematic review and proposed codification of definitions. *Diabetes Metab Res Rev.* 2015;31(7):680-690.

233. Cyganek K, Hebda-Szydlo A, Skupien J, et al. Postpregnancy Glycemic Control and Weight Changes in Type 1 Diabetic Women. *Diabetes Care.* 2013;36(5):1083-1087.

234. Gold AE, Reilly C, Walker JD. Transient improvement in glycemic control. The impact of pregnancy in women with IDDM. *Diabetes Care.* 1998;21(3):374-378.

235. Nielsen LR, Ekbom P, Damm P, et al. HbA1c levels are significantly lower in early and late pregnancy. *Diabetes Care.* 2004;27(5):1200-1201.

236. Linné Y, Dye L, Barkeling B, Rössner S. Long-term weight development in women: a 15-year follow-up of the effects of pregnancy. *Obes Res.* 2004;12(7):1166-1178.

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Appendix 3 continued

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Appendix 4: Core Outcome Set – Standards for Reporting: The COS-STAR Statement[210]

SECTION/TOPIC	ITEM No.	CHECKLIST ITEM
TITLE/ABSTRACT		
Title	1a	Identify in the title that the paper reports the development of a COS
Abstract	1b	Provide a structured summary
INTRODUCTION		
Background and Objectives	2a	Describe the background and explain the rationale for developing the COS.
	2b	Describe the specific objectives with reference to developing a COS.
Scope	3a	Describe the health condition(s) and population(s) covered by the COS.
	3b	Describe the intervention(s) covered by the COS.
	3c	Describe the setting(s) in which the COS is to be applied.
METHODS		
Protocol/Registry Entry	4	Indicate where the COS development protocol can be accessed, if available, and/or the study registration details.
Participants	5	Describe the rationale for stakeholder groups involved in the COS development process, eligibility criteria for participants from each group, and a description of how the individuals involved were identified.
Information Sources	6a	Describe the information sources used to identify an initial list of outcomes.
	6b	Describe how outcomes were dropped/combined, with reasons (if applicable).
Consensus Process	7	Describe how the consensus process was undertaken.
Outcome Scoring	8	Describe how outcomes were scored and how scores were summarised.
Consensus Definition	9a	Describe the consensus definition.
	9b	Describe the procedure for determining how outcomes were included or excluded from consideration during the consensus process.
Ethics and Consent	10	Provide a statement regarding the ethics and consent issues for the study.
RESULTS		
Protocol Deviations	11	Describe any changes from the protocol (if applicable), with reasons, and describe what impact these changes have on the results.
Participants	12	Present data on the number and relevant characteristics of the people involved at all stages of COS development.
Outcomes	13a	List all outcomes considered at the start of the consensus process.
	13b	Describe any new outcomes introduced and any outcomes dropped, with reasons, during the consensus process.
COS	14	List the outcomes in the final COS.
DISCUSSION		
Limitations	15	Discuss any limitations in the COS development process.
Conclusions	16	Provide an interpretation of the final COS in the context of other evidence, and implications for future research.
OTHER INFORMATION		
Funding	17	Describe sources of funding/role of funders.
Conflicts of Interest	18	Describe any conflicts of interest within the study team and how these were managed.