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# Retrospective national cohort study of pregnancy outcomes for women with type 1 and type 2 diabetes mellitus in Republic of Ireland

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*Abbreviations:* PPC, Pre-pregnancy Clinic; LGA, Large for Gestational Age; HbA1c, Haemoglobin A1c; DPSG, Diabetes Prevention Study Group; PGDM, Pre-gestational Diabetes Mellitus; RoI, Republic of Ireland; BMI, Body Mass Index; EmCS, Emergency Caesarean Section; PET, Pre-eclampsia; PIH, Pregnancy Induced Hypertension; SGA, Small for Gestational Age; NICU, Neonatal Intensive Care Unit; LADA, Latent Autoimmune Diabetes of Adulthood; MODY, Maturity Onset Diabetes of the Young; LMP, Last Menstrual Period; EHR, Electronic Health Record; CSII, Continuous Subcutaneous Insulin Infusion; CGM, Continuous Glucose Monitoring; ELCS, Elective Caesarean Section; IOM, Institute of Medicine.

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ABSTRACT

*Aim:* Report the outcomes of pregnant women with type 1 and type 2 diabetes and to identify modifiable and non-modifiable factors associated with poor outcomes.
*Methods:* Retrospective analysis of pregnancy preparedness, pregnancy care and outcomes in the Republic of Ireland from 2015 to 2020 and subsequent multivariate analysis.
*Results:* In total 1104 pregnancies were included. Less than one third attended pre-pregnancy care (PPC), mean first trimester haemoglobin A1c was 7.2 ± 3.6% (55.5 ± 15.7 mmol/mol) and 52% received pre-conceptual folic acid. Poor preparation translated into poorer pregnancy outcomes. Livebirth rates (80%) were comparable to the background population however stillbirth rates were 8.7/1000 (four times the national rate). Congenital anomalies occurred in 42.5/1000 births (1.5 times the background rate). More than half of infants were large for gestational age and 47% were admitted to critical care. Multivariate analyses showed strong associations between non-attendance at PPC, poor glycaemic control and critical care admission (adjusted odds ratio of 1.68 (1.48–1.96) and 1.61 (1.43–1.86), $p < 0.05$ respectively) for women with type 1 diabetes. Smoking and teratogenic medications were also associated with critical care admission and hypertensive disorders of pregnancy.
*Conclusion:* Pregnancy outcomes in women with diabetes are suboptimal. Significant effort is needed to optimize the modifiable factors identified in this study.

## 1. Introduction

Diabetes mellitus is one of the most common medical complications of pregnancy. Women with a diagnosis of diabetes experience higher rates of hypertensive disorders; pre-term delivery; large for gestational age (LGA) infants; Caesarean section, and stillbirth [1]. Prevention of such adverse outcomes is more important than ever as the prevalence of diabetes continues to rise globally and a substantial increase in the number of pregnancies affected by pre-gestational diabetes has been observed over the past 15 to 20 years [2]. Although this increase is multi-factorial, it is primarily driven by the substantial increase in obesity and type 2 diabetes in adolescents and young adults [3].

Outside of the immediate peri-natal period, infants of women with diabetes may face complications in later life. Macrosomic and LGA infants have adverse cardiometabolic profiles in adulthood and the rates of congenital anomalies are higher in women with diabetes compared to the background population [4,5].

It is widely appreciated that the risk of congenital anomaly increases with pre-pregnancy glucose levels and haemoglobin A1c (HbA1c) and patients are advised to enter pregnancy with optimal glycaemic control [6]. International guidelines recommend a pre-pregnancy target HbA1c of <6.5% (48 mmol/mol) [7].

Although both type 1 and type 2 diabetes pose a risk during pregnancy and have similar treatment targets, they are unique clinical entities associated with different disease profiles. Women with type 1 diabetes are more likely to undergo emergency delivery via Caesarean section and have a higher incidence of infant hypoglycaemia [8]; while women with type 2 diabetes face higher rates of congenital anomalies and neonatal death [1].

In an effort to reduce such complications a number of published studies have described efforts taken to improve pre-pregnancy care and outcomes for women with diabetes [9,10]. While outcomes for women with diabetes have improved over time, they still do not match the outcomes of women with normal glucose tolerance [8,11].

To capture improvements and identify ongoing deficits in care the Diabetes in Pregnancy Study Group (DPSG) listed annual national audits of women with pre-gestational diabetes as one of its key priorities [12]. A number of countries have adhered to this recommendation including Ireland which has published its data since 2015 [13–15].

The aim of this retrospective cohort study is two-fold-; firstly to report the outcomes of over 1000 pregnancies affected by pre-gestational diabetes mellitus (PGDM) throughout the Republic of Ireland (RoI) over a 5 year period from 2015 to 2020, comparing the outcomes of type 1 diabetes and type 2 diabetes to assess if differences identified in previous studies remain consistent. Secondly, to examine modifiable and non-modifiable factors associated with adverse pregnancy outcomes for both type 1 diabetes and type 2 diabetes.

## 2. Materials and methods

### 2.1. Study design

Ethical approval was granted by Galway University Hospital (CA 2488). Data were collected from hospitals providing care to women with diabetes within the RoI. All twenty antenatal centres were invited to participate. We included all women with a singleton pregnancy and a diagnosis of type 1, type 2, monogenic or secondary diabetes who had an estimated delivery date between 1st January 2015 and 31st December 2020. We excluded women with twin pregnancies and those who had diabetes for less than six months prior to their last menstrual period (LMP).

Each centre collected data independently either from paper based or electronic health records (EHR) and submitted it to the study co-ordinator via a pre-designed data collection tool. Data were collected on pregnancy preparedness and pre-conceptual glycaemic control; pregnancy complications including hypertensive disorders and hospital admissions; pregnancy and delivery outcomes and neonatal outcomes. A full list of all collected data and the definitions used can be found in the supplementary data. In the event of uncertainty, the study co-ordinator (CN) classified outcomes.

Data were analysed using SPSS version 25 software. Categorical variables were presented as n (%); normally distributed, continuous variables were analysed as mean ± standard deviation and skewed data were presented as median (interquartile range).

Outcomes were assessed for the entire population, however due to the small number of monogenic and secondary cases, comparisons of significance were only performed on women with type 1 and type 2 diabetes. The outcomes of women with type 1 and type 2 diabetes were compared using unpaired t-tests (for data of equal variance and normal distribution) and using the Mann-Whitney test for non-parametric data. Sample proportions were compared using Fisher's exact analysis. We also conducted analyses to review differences in pregnancy outcomes between centres with >2000 deliveries per year versus those with <2000 deliveries per year.

To identify modifiable and non-modifiable risk factors associated with adverse pregnancy outcomes binary logistic analyses were performed. Modifiable risk factors considered were HbA1c levels, body mass index (BMI), smoking status, use of teratogenic medications and attendance for pre-pregnancy care. Non-modifiable risk factors included ethnicity, diabetes type and pre-pregnancy diabetes related complications. Non-modifiable confounders included maternal age and duration of diabetes were also considered. Adverse pregnancy outcomes included emergency caesarean section (EmCS), preeclampsia (PET), pregnancy-associated hypertension (PIH), stillbirth, congenital malformation, preterm birth (birth at <37 weeks of gestation), large (LGA) and small

for gestational age (SGA) and neonatal intensive care unit (NICU) admission. Given the extremely small numbers of neonatal deaths in the first 28 days of life (n = 2) perinatal mortality was not calculated as a separate adverse outcome.

## 3. Results

Eighteen out of twenty centres participated, and data were collected on 1104 pregnancies. Fifty-eight pregnancies were excluded due to duration of diabetes of <6 months (n = 26); twelve women received a diagnosis of diabetes during pregnancy; eight women had twin pregnancies and the remainder had insufficient pregnancy and delivery information to be included (n = 12).

### 3.1. Cohort characteristics (Table 1 and Table 2)

The majority of women had type 1 diabetes (n = 694, 66.2%) including latent autoimmune diabetes in adults (LADA)(n = 2). In line with our previous published work these cohorts were analysed together (n = 696, 63.2%) [14,15]. Just over one third of women had type 2 diabetes (n = 374, 33.8%). The remaining 34 women had a diagnosis of "other, including twenty-five women with maturity onset of diabetes of the young (MODY), four with diabetes secondary to pancreatitis, three with post-transplant diabetes and 2 with cystic fibrosis related diabetes – all 34 were included in the total cohort analysis.

Women with type 1 diabetes were younger (31.7 ± 7.5 versus 34.4 ± 5.8 years, p < 0.05), more likely to be Caucasian (92.4% versus 63.6%, p < 0.05), with a longer duration of diabetes (15.1 ± 8.6 versus 5.6 ± 3.2 years, p < 0.05) and a higher burden of microvascular complications including retinopathy (27.0% versus 2.9%, p < 0.05) and microalbuminuria (13.8% versus 7.3%, p < 0.05) entering pregnancy. Women with type 1 diabetes had a lower mean BMI (26.8 ± 5.3 versus 33.4 ± 7.6 kg/m$^2$, p < 0.05). Twenty per cent of women in both groups exceeded the Institute of Medicine's (IoM) recommendations for weight gain in pregnancy (depicted in Table 2).

### 3.2. Pregnancy preparedness (Table 1)

More women with type 1 diabetes than type 2 diabetes attended PPC (32.9% vs 25.9%, p < 0.05). Pre-pregnancy use of 5 mg folic acid was more commonly seen in those with type 1 diabetes (55.3% vs 47.7%, p < 0.05). Current use of teratogenic medications was similar between groups (5.8% versus 8.9%, p = 0.06). Women with type 1 diabetes entered pregnancy with a significantly higher HbA1c compared to those with type 2 diabetes (7.8 ± 3.8 vs 7.1 ± 3.8% (61.9 ± 18.5 vs 53.9 ± 17.2 mmol/mol), p < 0.05). Using 5 mg folic acid use, no teratogenic medication use and a first trimester HbA1c of ≤6.5% (48 mmol/mol) as requirements for adequate pregnancy preparation, only 16% of women were well prepared for pregnancy and this was consistent across type 1 and type 2 diabetes.

### 3.3. Pregnancy course (Tables 2 and 3)

During the first trimester more women with type 1 diabetes received 5 mg folic acid than those with type 2 diabetes (79.1% vs 71.2%, p < 0.05). Eleven per cent of the total cohort continued to smoke. Glycaemic control improved for both groups in the second and third trimesters. As in the pre-pregnancy phase, women with type 2 diabetes had a lower HbA1c than those with type 1 diabetes throughout pregnancy (for example in the third trimester, the mean HbA1c for women with type 1 diabetes was 6.5 ± 3.1% (46.8 ± 9.9 mmol/mol) versus 5.9 ± 2.9% (40.8 + 8.4 mmol/mol) for women with type 2 diabetes (p < 0.05). A small number of women with type 1 diabetes (n = 91, 13.1%) used continuous subcutaneous insulin infusion (CSII therapy). CSII users were older with a longer duration of disease (34.3 ± 4.5 versus 31.4 ± 3.7 years, p < 0.05 and 19.1 ± 9.3 versus 14.9 ± 8.4 years, p < 0.05 respectively). They had better glycaemic control in the pre-pregnancy period and in the first and second (but not the third) trimesters and a reduced risk of prematurity (8.2% versus 24.2%, p < 0.05). Despite the improvement in glycaemic control, CSII users had a higher rate of congenital anomaly (9.6% versus 3.3%, p < 0.05).

For the first time in this cohort, we were able to gather data on continuous glucose monitoring (CGM) usage. In women with type 1 diabetes from 1st January 2019 to 31st December 2020 (n = 161), 30.4% (n = 49) used CGM and a further 17 (10.6%) used intermittent CGM.

**Table 1**
Patient demographics and pregnancy preparation.

| | All patients n = 1104 | Type 1 diabetes n = 696 | Type 2 diabetes n = 374 | p value |
|---|---|---|---|---|
| **Age (years)** | 32.7 ± 5.9 | 31.7 ± 5.7 | 34.4 ± 5.8 | <0.05 |
| **Caucasian ethnicity** | 911 (82'9%) | 643 (92.4%) | 236 (63.6%) | <0.05 |
| **BMI (kg/m$^2$)** | 28.9 ± 7.1 | 26.8 ± 5.3 | 33.4 ± 7.6 | <0.05 |
| **BMI 18–24.9 (kg/m$^2$)** | 306 (27.7) | 253 (36.4%) | 37 (10.0%) | <0.05 |
| **BMI 25–30 (kg/m$^2$)** | 280 (25.3%) | 209 (30.0%) | 62 (16.2%) | <0.05 |
| **BMI 30–35 (kg/m$^2$)** | 188 (17.1) | 89 (12.8%) | 98 (26.4%) | <0.05 |
| **BMI 35–40 (kg/m$^2$)** | 81 (7.4%) | 24 (3.4%) | 56 (15.1%) | <0.05 |
| **BMI > 40 (kg/m$^2$)** | 68 (6.2%) | 13 (1.9%) | 55 (14.8%) | <0.05 |
| **Duration of DM (years)** | 12.2 ± 8.9 | 15.1 ± 8.6 | 5.6 ± 3.2 | <0.05 |
| **Gravidity** | 2.6 | 2.3 | 3.1 | <0.05 |
| **Parity** | 1.1 | 0.9 | 1.4 | <0.05 |
| **Retinopathy** | 208 (18.8) | 188 (27.0%) | 11 (2.9%) | <0.05 |
| **Hypertension** | 124 (11.3%) | 63 (9.1%) | 57 (15.4%) | <0.05 |
| **Microalbuminuria** | 131 (11.9%) | 96 (13.8%) | 27 (7.3%) | <0.05 |
| **PPC attendance** | 335 (30.5%) | 229 (32.9%) | 96 (25.9%) | <0.05 |
| **5 mg folic acid usage** | 490 (44.5%) | 340 (48.9%) | 134 (36.1%) | <0.05 |
| **Teratogenic meds** | 73 (6.6%) | 41 (5.9%) | 33 (8.9%) | 0.06 |
| **Pre-pregnancy HbA1c (mmol/mol)** | 59.1 ± 18.3 | 61.9 ± 18.5 | 53.9 ± 17.2 | <0.05 |
| **HbA1c (%)** | 7.5 ± 3.8 | 7.8 ± 3.8 | 7.1 ± 3.7 | |
| **Well prepared 3 criteria** | 182 (16.6%) | 117 (16.8%) | 58 (15.6%) | 0.61 |

BMI = body mass index; PPC = pre-pregnancy clinic; HbA1c = haemoglobin A1c; IOM = institute of medicine; MDI = multiple daily injection; CSII = continuous subcutaneous insulin injection; Well prepared = a pre-pregnancy HbA1c of ≤6.5% (48 mmol/mol), the use of 5 mg folic acid pre-conceptually and the absence of any teratogenic medication use

### 3.4. Pregnancy outcome (Table 4)

The majority of women in our cohort had a livebirth (80%), however eight stillbirths were reported (8.69 per 1000 total births; 6.86 per 1000 total births in type 1 diabetes and 9.71 per 1000 total births in type 2 diabetes) (Table 4).

In respect to delivery and pregnancy outcome, 35% of women underwent elective Caesarean sections (ELCS) and a further 32% and 23% of type 1 and type 2 diabetes respectively required EmCS (p < 0.05). More women with type 1 diabetes had a pre-term birth at <37 weeks (30.4% vs 20.7%; p < 0.05) and more than half of infants of mothers with type 1 diabetes were admitted to NICU. More than 50% of infants were born LGA with a small number born SGA (1.1%).

The rate of congenital anomaly observed was 42.5 and 51.5 per 1000

**Table 2**
Glycaemic control and pregnancy course.

| | All patients n = 1104 | Type 1 diabetes n = 696 | Type 2 diabetes n = 374 | p value |
|---|---|---|---|---|
| 1st trimester HbA1c (mmol/mol) | 55.5 ± 15.7 | 58.2 ± 16.2 | 50.1 ± 14.5 | <0.05 |
| HbA1c (%) | 7.2 ± 3.6 | 7.5 ± 3.6 | 6.7 ± 3.5 | |
| 1st trimester HbA1c ≤ 48 mmol/mol (6.5%) | 335 (30.5%) | 167 (24.0%) | 137 (36.9%) | <0.05 |
| 1st trimester HbA1c ≥ 86 mmol/mol (10%) | 56 (5.1%) | 45 (6.5%) | 10 9 (2.7%) | <0.05 |
| Booking < 8 weeks | 475 (43.2%) | 358 (51.5%) | 52 (14.0%) | <0.05 |
| GWG above IOM recommendations | 19.2% | 19.2% | 21.0% | 0.52 |
| Weight gain (kg) | 5.50 ± 7.1 | 6.2 ± 7.5 | 4.5 ± 6.4 | <0.05 |
| Diet only | 24 (2.2%) | 0 (0%) | 20 (5.4%) | <0.05 |
| Metformin only | 140 (12.6%) | 0 (0%) | 137 (36.4%) | <0.05 |
| Insulin + metformin | 130 (11.7%) | 33 (4.7%) | 96 (25.6%) | <0.05 |
| CSII | 91 (8.2%) | 91 (13.1%) | 0 (0.5) | <0.05 |
| Other | 16 (1.5%) | 1 (0.1%) | 13 (3.5%) | <0.05 |
| MDI | 653 (59.3%) | 555 (79.7%) | 80 (21.3%) | <0.05 |
| 1st trimester 5 mg folic acid use | 840 (76.3%) | 550 (79.1%) | 264 (71.2%) | <0.05 |
| 2nd Trimester HbA1c (mmol/mol) (%) | 44.6 ± 10.1 6.2 ± 3.1 | 47.4 ± 10.0 6.5 ± 3.1 | 39.5 ± 8.1 5.8 ± 2.9 | <0.05 |
| 3rd trimester HbA1c (mmol/mol) (%) | 44.8 ± 9.9 6.3 ± 3.1 | 46.8 + 9.9 6.4 ± 3.1 | 40.8 ± 8.4 5.9 ± 2.9 | <0.05 |
| Smoking during pregnancy | 122 (11.1%) | 76 (10.9%) | 40 (10.8%) | 0.96 |
| Hospitalisation during pregnancy | 564 (51.0%) | 360 (51.7%) | 190 (50.7%) | 0.76 |
| Average no of hospitalisations | 1.5 | 1.6 | 1.3 | <0.05 |

GWG = gestational weight gain; IOM = institute of medicine; CSII = continuous subcutaneous insulin infusion; MDI = multiple daily injection.

in women with type 1 and type 2 diabetes respectively. Stillbirth rates were 6.86 and 9.71 per 1000 in women with type 1 and type 2 diabetes respectively. In total, two neonatal deaths were recorded.

### 3.5. Predictors of adverse outcomes

An unadjusted binary logistic analysis of the entire cohort was performed. There is a strong body of evidence to support an increased risk of adverse pregnancy outcome with a HbA1c of >6.5% (48 mmol/mol), however we noted that only one third of our patients met this target. Nearly half (42%) of women had a pre-pregnancy HbA1c of >7% (53 mmol/mol). While this is considered good control outside of pregnancy, we wanted to analyse the risk of maternal and foetal complications at this level to determine the risks for entering pregnancy with even slightly sub-optimal control. As such we chose a pre- and early pregnancy HbA1c of >7% (53 mmol/mol) as a modifiable risk factor. Smoking, teratogenic medication use, BMI of >30 kg/m$^2$ and non-attendance for pre-pregnancy care are all associated with poor pregnancy outcomes and were considered modifiable risk factors [16–19].

Non-modifiable risk factors included non-Caucasian ethnicity, diabetes type, and pre-pregnancy diabetes related complications. Other factors such as maternal age and duration of diabetes have been shown to increase the risk of vasculopathy, prematurity and severe hypoglycaemia and were thus considered confounders which were included in a multivariate regression model [20].

**Table 3**
Demographics and outcomes for CSII users.

| | CSII (n = 91) | Non-CSII (n = 605) | p value |
|---|---|---|---|
| Age (years) | 34.3 (4.5) | 31.4 (3.7) | <0.05 |
| Caucasian ethnicity | 89 (97.8%) | 558 (92.2%) | 0.05 |
| BMI (kg/m$^2$) | 26.6 (4.9) | 26.8 (5.4) | 0.67 |
| BMI 18–24.9 (kg/m$^2$) | 38 (41.8%) | 215 (35.5%) | 0.24 |
| BMI 25–30 (kg/m$^2$) | 24 (26.4%) | 185 (30.6%) | 0.41 |
| BMI 30–35 (kg/m$^2$) | 14 (15.4%) | 75 (12.4%) | 0.42 |
| BMI 35–40 (kg/m$^2$) | 5 (5.5%) | 20 (3.3%) | 0.29 |
| BMI > 40 (kg/m$^2$) | 1 (1.1%) | 12 (2.0%) | 0.56 |
| Duration of DM (years) | 19.1 (9.3) | 14.9 (8.4) | <0.05 |
| Retinopathy | 23 (25.3%) | 164 (27.1%) | 0.72 |
| Hypertension | 14 (15.4%) | 49 (8.1%) | 0.02 |
| PPC attendance | 42 (46.2%) | 188 (31.1%) | <0.05 |
| 5 mg folic acid usage | 61 (67.0%) | 280 (46.3%) | <0.05 |
| Teratogenic meds | 7 (7.7%) | 27 (4.5%) | 0.19 |
| Pre-pregnancy HbA1c (mmol/mol) | 55.3 ± 12.2 | 62.8 ± 19.1 | <0.05 |
| 1st trimester HbA1c (mmol/mol) | 53.1 ± 11.4 | 59.2 ± 16.7 | <0.05 |
| 1st trimester HbA1c ≤ 48 mmol/mol (6.5%) | 27 (29.7%) | 141 (23.3%) | 0.18 |
| 1st trimester HbA1c ≥ 86 mmol/mol (10%) | 1 (1.1%) | 40 (6.6%) | <0.05 |
| Booking < 8 weeks | 56 (61.5%) | 334 (55.2%) | 0.26 |
| GWG above IOM recommendations | 21 (28.8%) | 114 (22.%) | 0.21 |
| 2nd Trimester HbA1c (mmol/mol) | 45.5 ± 8.6 | 47.9 ± 10.3 | P < 0.05 |
| 3rd trimester HbA1c (mmol/mol) | 44.9 ± 8.4 | 47.3 ± 10.2 | 0.12 |
| Smoking during pregnancy | 4 (4.4%) | 72 (11.9%) | <0.05 |
| Livebirth | 73 (80.2%) | 509 (84.0%) | 0.36 |
| Stillbirth | 0 (0.0%) | 4 (0.7%) | 0.42 |
| Miscarriage | 18 (19.8%) | 87 (14.4%) | 0.18 |
| Termination | 0 (0%) | 5 (0.8%) | 0.39 |
| NVD | 19 (26.0%) | 103 (20.1%) | 0.24 |
| ELCS | 30 (41.1%) | 190 (37.0%) | 0.49 |
| EmCS | 19 (26.0%) | 169 (32.9%) | 0.24 |
| Gestation at delivery | 37.7 ± 1.9 | 37.0 ± 2.5 | 0.12 |
| Preterm < 37 weeks | 6 (8.2%) | 124 (24.2%) | <0.05 |
| NICU admission | 34 (46.6%) | 285 (55.6%) | 0.14 |
| Congenital anomaly | 7 (9.6%) | 17 (3.3%) | <0.05 |
| Birth weight (kg) | 3.5 ± 0.8 | 3.5 ± 0.77 | 0.82 |
| Birth weight > 4 kg | 20 (27.4%) | 141 (27.5%) | 0.98 |
| Birth weight > 4.5 kg | 8 (11.0%) | 47 (9.2%) | 0.62 |
| SGA | 1 (1.4%) | 4 (0.8%) | 0.61 |
| LGA | 43 (58.9%) | 298 (58.1%) | 0.89 |

CSII = Continuous subcutaneous insulin infusion; BMI = body mass index; PPC = pre-pregnancy clinic; GWG = gestational weight gain; IOM = institute of medicine; NVD = normal vaginal delivery; ELCS = elective Caesarean section; EmCS = emergency Caesarean section; SGA = small for gestational age; LGA = large for gestational age

### 3.6. Modifiable risk factors

After adjusting for maternal age >30 years, diabetes duration of >10 years and other confounders (specific to each adverse outcome) several significant associations were identified. An elevated pre- and early pregnancy HBA1c, cigarette smoking and non-attendance at a PPC were all significantly associated with an increased risk of NICU admissions (adjusted odds ratios (ORs) of 1.6 (95% CI 1.46–1.83); 1.63 (95% CI 1.48–1.83); 1.61 (95% CI 1.42–1.89) and 1.87 (95% CI 1.41–2.29), p < 0.05 respectively).

In women with type 1 diabetes poor glycaemic control, smoking, non-attendance at PPC and teratogenic medication use were all associated with adverse outcomes (detailed analysis given in Table 5).

For women with type 2 diabetes we identified fewer statistically significant associations. A maternal BMI of >30 kg/m$^2$ was associated with a higher risk of hypertensive disorders of pregnancy, however this did not remain significant after adjusting for confounders.

Additionally, although a BMI of ≥30 kg/m$^2$ was not associated with adverse outcomes, gestational weight gain above the IOM recommendations was associated with a decreased risk of EmCS (in an unadjusted

**Table 4**
Delivery and pregnancy outcome.

| | All patients n = 1104 | Type 1 diabetes n = 696 | Type 2 diabetes n = 374 | p value |
|---|---|---|---|---|
| **Livebirth** | 917 (83.0%) | 580 (83.3%) | 309 (82.5%) | 0.74 |
| **Stillbirth** | 8 (0.7%) | 4 (0.6%) | 3 (0.8%) | 0.70 |
| **Miscarriage** | 167 (15.2%) | 104 (15.0%) | 58 (15.6%) | 0.79 |
| **Termination** | 7 (0.6%) | 5 (0.7%) | 2 (0.5%) | 0.69 |
| **NVD** | 244 (26.4%) | 122 (20.9%) | 105 (33.7%) | <0.05 |
| **ELCS** | 325 (35.2%) | 209 (35.7%) | 209 (35.3%) | 0.91 |
| **EmCS** | 263 (28.5%) | 188 (32.2%) | 74 (23.6%) | <0.05 |
| **Unknown** | 15 (1.65) | 9 (1.5%) | 5 (1.6%) | 0.91 |
| **Gestation at delivery** | 37.2 ± 2.7 | 36.9 + 2.7 | 37.7 ± 2.6 | <0.05 |
| **Preterm < 37 weeks** | 249 (27.1%) | 177 (30.4%) | 64 (20.7%) | <0.05 |
| **NICU admission** | 433 (46.7%) | 318 (54.4%) | 111 (35.3%) | <0.05 |
| **Congenital anomaly*** | 41 (4.4%) | 25 (4.3%) | 16 (5.1%) | 0.56 |
| **Birth weight > 4 kg** | 210 (22.6%) | 161 (27.6%) | 45 (13.9%) | <0.05 |
| **Birth weight > 4.5 kg** | 65 (7.1%) | 55 (9.4%) | 10 (3.2%) | <0.05 |
| **SGA** | 8 (0.9%) | 5 (0.9%) | 3 (1.0%) | 0.88 |
| **LGA** | 481 (52.1%) | 341 (58.5%) | 131 (41.7%) | <0.05 |

*= calculated by livebirth, stillbirth and terminations.
NVD = normal vaginal delivery; ELCS = Elective Caesarean Section; EmCS = Emergency Caesarean Section; SGA = small for gestational age; LGA = large for gestational age.

**Table 5**
Unadjusted and adjusted analysis for women with type 1 diabetes.

| | Unadjusted OR | Adjusted OR |
|---|---|---|
| **Pre-pregnancy HbA1c > 53 mmol/mol (7%)** | | |
| NICU admission * | 2.3 (1.56–3.4) | 1.59 (1.40–1.85) |
| Hypertensive disorders of pregnancy ‡ | 2.18 (1.18–4.03) | 1.38 (1.19–1.69) |
| **Early pregnancy HbA1c > 7% (53 mmol/mol)** | | |
| LGA infant † | 1.47 (1.03–2.09) | 1.69 (1.50–1.97) |
| NICU admission * | 1.99 (1.39–2.85) | 1.61 (1.43–1.86) |
| **Smoking** | | |
| NICU admission * | 1.74 (1.03–2.92) | 1.57 (1.34–1.92) |
| **Teratogenic medication** | | |
| Hypertensive disorders of pregnancy ‡ | 3.08 (1.50–6.33) | 1.23 (1.13–1.47) |
| **Non-attendance at PPC** | | |
| Delivery before 37 weeks' gestation * | 2.23 (1.56–3.32) | 1.38 (1.26–1.55) |
| NICU admission * | 1.93 (1.36–2.73) | 1.68 (1.48–1.96) |

*= adjusted for maternal age >30 years, duration of diabetes >10 years and hypertensive disorders of pregnancy.
†= adjusted for maternal age >30 years, duration of diabetes >10 years and BMI ≥ 30 kg/m$^2$.
‡= adjusted for maternal age >30 years, duration of diabetes >10 years and pre-pregnancy hypertension
NICU = Neonatal Intensive Care Unit; LGA = Large for Gestational Age.

analysis). This reduction was explained by an increased rate of ELCS in women with excessive gestational weight gain.

Finally, in the overall cohort there was no difference observed between weight gain above the IOM recommendations and a composite endpoint of EmCS, hypertension, stillbirth, congenital anomaly, preterm birth, LGA/SGA or NICU admissions (OR 0.93 (95% CI 0.51–1.71, p = 0.83).

### 3.7. Non-modifiable risk factors

In an unadjusted analysis evaluating the impact of ethnicity, Caucasian women had a lower risk of LGA infants. Caucasian women with type 1 diabetes had a lower risk of NICU admission and Caucasian women with type 2 diabetes had a higher risk of premature delivery. We also identified an increased risk of NICU admission and LGA birth in women with type 1 diabetes and microvascular complications. However, none of the above associations remained significant after adjusting for confounders.

Given recent evidence which linked metformin usage with SGA infants we assessed our rates of SGA births in infants exposed to metformin in utero. We did not find any association between metformin exposure and SGA births (OR 1.91 95% CI 0.57–7.58, p = 0.36).

### 3.8. Centre differences

We further analysed centres according to number of deliveries per year. In total twelve centres had <2000 deliveries per year and 6 centres had >2000 per year. Women attending smaller centres were younger, more likely to be overweight (but not obese) and had worse glycaemic control before and during pregnancy. The same cohort were more likely to have retinopathy entering pregnancy and required more admissions during pregnancy.

Fewer women attending smaller centres accessed PPC and fewer took folic acid at the correct dose – a trend which continued into pregnancy. Women in smaller centres had more pre-term births and a higher rate Caesarean section. These women were also significantly more likely to have infants weighing >4 kg and >60% of infants in smaller centres were admitted to the NICU. Further details are available in supplementary data.

## 4. Discussion

This study is the largest evaluation of pre-gestational diabetes ever conducted in the RoI and has built on previously published work which highlighted the adverse outcomes faced by women with pregestation diabetes [1,14,15]. It provides key data on an underserved group whose outcomes lag behind women with normal glucose tolerance despite the targets of the St Vincent's declaration of 1989 [21]. Furthermore, this cohort study is in line with the DPSG key "challenges for the next decade" which sets the use of "national pre-gestational diabetes audit" as one of its key targets [12].

### 4.1. Cohort characteristics and pregnancy preparedness

This work supports other published data which found that women with type 2 diabetes are older; have a higher BMI; are more likely to enter pregnancy on teratogenic medication and have higher rates of pre-pregnancy hypertension than women with type 1 diabetes [13].

There is clear evidence that our patient demographic is changing and there is geographical variation. In 2015, type 2 diabetes accounted for 30% of cases of pre-gestational diabetes and this figure now approaches 34% [14]. While this rate is close to that seen in other large obstetrics centres in Ireland, it differs from a 2014 study from the west of Ireland which found that type 2 diabetes made up 40% of all pre-gestational cases[22,11]. Our evaluation of smaller versus larger centres also found that there is a 4% difference between larger (mostly urban) and

smaller centres in rates of type 2 diabetes.

It is also noteworthy that more than 50% of women with type 1 diabetes have a BMI above 24.9 kg/m$^2$ which is reflective of increased obesity rates in diabetes. The combined adverse neonatal effects of maternal obesity and diabetes are well described [18]. While the need to reduce obesity levels in adults with diabetes is recognised, many pharmacological methods which are effective in other groups are not suitable for those planning pregnancy [23].

### 4.2. Pregnancy outcomes

We noted high rates of operative delivery (>63%). A high rate of Caesarean delivery could be partly explained by the high rates of macrosomia and LGA infants seen in women with type 1 diabetes. While the rate of LGA infants is similar to the United Kingdom, rates of SGA are significantly lower in our cohort for both women with type 1 diabetes and type 2 diabetes. SGA birth rates accounted for <1% in each group and these rates are considerably lower than those observed in other countries. The low rate in our cohort is unexplained, however rates of SGA vary according to the defining criteria and rates of 1.3–8.9% (depending on the method used) are seen in women with type 1 diabetes [24].

A key predictor of foetal size is gestational weight gain. In non-diabetic women gestational weight gain above the IOM recommendation is associated with Caesarean delivery and LGA infants. In women with diabetes increased gestational weight gain increases the risk of a LGA birth independent of glycaemic control [25].

We found that nearly 20% of women had a gestational weight gain which exceeded IOM recommendations. This rate is significantly lower than the rates described in other patients with diabetes. In particular the weight gain observed in women with type 2 diabetes is less than that described in other studies [26].

In this cohort neither obesity nor excessive gestational weight gain increased the risk of stillbirth or congenital anomaly- however rates of both exceeded the rates observed in the background population (26 per 1000 births for congenital anomaly and 3.54 per 1000 for stillbirth).

### 4.3. Regression analysis

The results of our regression analysis also revealed several important results, most especially the strong association with adverse outcomes and modifiable risk factors including early glycaemia control, smoking, teratogenic medication use and PPC attendance. Similar results have been observed in other studies however unlike other papers we did not identify any significant associations in women with type 2 diabetes [1].

After adjusting for confounders, diabetes type was the only non-modifiable risk associated with adverse outcomes. These findings mirror results from other countries and highlight the importance of pregnancy planning and early intervention.

Our study demonstrates that PPC attendance is the key intervention- it provides the opportunity to target issues like smoking, inappropriate medication usage and to optimise glycaemic control.

Factors which limit clinic attendance include social demographics, poor patient and physician awareness and fear of the unknown [27]. Women attending PPC are more likely to be in a stable relationship, have a higher income and have type 1 diabetes [28].

Currently over half of pregnancies remain unplanned. Unplanned pregnancies are more common in younger women, certain ethnic minorities and those with a lower income [29]. As young adulthood is often a challenging time for diabetes control, multiple studies have evaluated methods to improve clinic attendance and glycaemic control [30].

To reduce unplanned pregnancies, clinicians should ensure contraception is a routine part of the diabetes consultation. Although the discussion of contraception is incorporated into best practice guidelines [31] many women report that contraception is not part of their consultation and many did not receive a comprehensive overview of their options [32].

Regardless of pre-pregnancy planning, once a pregnancy is confirmed strict glycaemic control is critical to assuring a positive outcome. Good glycaemic control can be achieved early in pregnancy in those who did not attend PPC provided they have early contact with ante-natal services [33]. Interventions like CGM are effective in improving glycaemic control and reducing NICU admissions- as the rate of CGM use is increasing in RoI this will be a feature of interest in future audits [34].

Outside of pregnancy, the use of CSII can improve HbA1c; however studies in pregnancy have shown that women changing from MDI to CSII may experience greater first trimester hyperglycaemia [35]. In our cohort, all patients on CSII had commenced treatment before pregnancy and despite better glycaemic control the only difference observed was in rates of pre-term births. Similar rates of NICU admission and infant size is potentially explained by the similar third trimester HbA1c between two groups.

In summary, it is significant that factors most strongly associated with poor maternal and foetal outcomes are modifiable, and the opportunity to initiate meaningful changes should not be missed.

### 4.4. Larger and smaller centres

Finally we evaluated the outcomes of women attending larger and small obstetric centres. There was a clear difference in the patient demographic and in pregnancy preparedness between women attending centres of different sizes. Throughout pregnancy women in larger centres had better glycaemic control and better rates of livebirth, miscarriage and stillbirth (non-significant). Rates of LGA, macrosomia, prematurity, NICU admission were all significantly better in larger centres. Similar results have been noted in other studies and some have suggested that care to women with diabetes in pregnancy should only be offered in large centres or in smaller centres where combined care is possible [36]. In other areas of endocrinology it has become standard practice to refer patients to a limited number of large volume centres and this has correlated positively with patient outcomes [37]. While women receiving their ante-natal care in larger centres may have better outcomes, there are a number of other factors to consider. Clinic attendance [38] and glycaemic control worsen in non-pregnant patients with diabetes when travel time to clinics is increased. In euglycaemic pregnant women, adverse outcomes increase with increased distance from an ante-natal unit [39].

As such any decision to centralise care for women with pre-gestational diabetes needs to consider the large body of evidence in this area

### 4.5. Limitations and strengths

This study has some limitations. It is a retrospective study which introduces the possibility of missing data. This undoubtedly affected our study as twelve patients were excluded due to poor data collection/unavailability of data. The majority of patients had one or more missing data parameter – the most commonly affected parameters were booking weight and BMI (15% of type 1 diabetes and 17.5% of type 2 diabetes were missing data on BMI). There is a risk of inadvertent patient omission - a particular concern in centres relying on paper-based records as miscarriages or early pregnancy losses may not be recorded.

There is also a lack of follow-on data for infants transferred outside of the hospital of birth. In our study we recorded only two neonatal deaths, giving a neonatal mortality rate of 2.2 per 1000 livebirths (which is similar to the rate of 2.5 per 1000 seen in the background population). This establishes the possibility of inaccurate information regarding neonatal death and highlights the need for detailed feedback to be made to the diabetic service in the referring hospital.

There are also no available data on social deprivation which has been associated with reduced rates of tight glycaemic control in women with

diabetes. This information is extremely informative in identifying high risk patients and should be a target for inclusion in future observational studies.

Finally, two large maternity centres did not participate. These centres manage complex diabetes cases and cases of foetal compromise from all over Ireland. Based on the number of deliveries per year in these two centres, we estimate that these centres would have contributed data on an additional 700 patients.

Our study also has a number of strengths. Firstly, it is a comprehensive data set of a national cohort with information on outcomes deemed important [40]. Secondly, we were able to include 90% of antenatal centres. Due to a high level of participant retention and engagement we expanded our data set to include more endpoints over time including length of NICU stay, maternal weight gain and CGM usage.

In summary this study provides information which has implications for health care providers and organisations involved in health care planning. It highlights the suboptimal preparation in the majority of women and underlines the importance of good glycaemic control, preconceptual folic acid use and the need for dedicated pre-pregnancy clinics to ensure patients' can enter pregnancy as prepared as possible to optimise their pregnancy outcomes.

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## 6. Contribution statement

C Newman, AM Egan and FP Dunne designed the project concept and data collection tool. CN collated the data and CN and AME performed statistical analysis. CN, AME and FPD drafted the original manuscript. All other authors were involved in data collected and the re-writing of the manuscript. All authors approved the final version of this manuscript.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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