Charles Darwin University

Real-world experience of metformin use in pregnancy

Observational data from the Northern Territory Diabetes in Pregnancy Clinical Register

on behalf of the Northern Territory Diabetes in Pregnancy Partnership

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A real-world experience of metformin use in pregnancy: observational data from the Northern Territory Diabetes in Pregnancy Clinical Register

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Running Title: Metformin use in pregnancy

Abstract

Background: In Australia's Northern Territory, Indigenous mothers account for 33% of births and have high rates of hyperglycaemia in pregnancy. Prevalence of type 2 diabetes in pregnancy is up to 10 times higher in Indigenous than non-Indigenous Australian mothers, and the use of metformin is common. We assessed birth outcomes in relation to metformin use during pregnancy from a clinical register.

Methods: Women with gestational diabetes (GDM), newly diagnosed diabetes in pregnancy (DIP), or pre-existing type 2 diabetes (T2DM) from 2012 to 2016 were included. Data were analysed for metformin use in the third trimester. Regression models were adjusted for maternal age, body mass index, parity and insulin use.

Results: Of 1649 pregnancies, 814 (49.4%) were to Indigenous women, of whom 234 (28.7%) had T2DM (vs 4.6% non-Indigenous women, p<0.001). Metformin use was high in Indigenous women (84-90% T2DM, 42-48% GDM/DIP) and increased over time in non-Indigenous women (43-100% T2DM, 14-35% GDM/DIP). There were no significant differences between groups with and without metformin for caesarean section [among Indigenous women with GDM/DIP with vs without metformin 51% vs 39%, adjusted OR(95% CI), 1.25(0.87, 1.81), p=0.22], large-for-gestational-age [24% vs 13%, adjusted OR, 1.5 (0.9, 2.5), p=0.1] or serious neonatal adverse events [9.4% vs 5.9%, adjusted OR, 1.32 (0.68, 2.57), p=0.42]. Metformin use was independently associated with earlier gestational age (37.7 weeks vs 38.5 weeks), however the risk did not remain independently higher after exclusion of women managed with medical nutrition therapy alone, and the increase in births <37 weeks was not significant on multivariate analysis [OR 1.68 (0.97, 2.92), p=0.61].

Conclusions: We found no clear evidence of any adverse outcomes related to the use of metformin for the treatment of hyperglycaemia in pregnancy.

Highlights

We report, from five years of real-world clinical register data, that use of metformin in pregnancy was high among Indigenous women and has increased from 2012 to 2016 among non-Indigenous women with type 2 diabetes and gestational diabetes in this remote region of Australia. We found no clear evidence of any adverse outcomes related to the use of metformin for the treatment of hyperglycaemia in pregnancy.

Keywords: gestational diabetes, metformin, diabetes in pregnancy, type 2 diabetes in pregnancy, birth outcomes

Introduction

Indigenous people experience disproportionately high rates of diabetes worldwide. Among Indigenous Australians, rates of type 2 diabetes are three times higher, and rates of type 2 diabetes in pregnancy over ten times higher, than for non-Indigenous Australians[1]. Hyperglycaemia in pregnancy (following the suggested classification of the International Federation of Gynaecology and Obstetrics (FIGO)[2]), including pre-existing diabetes, diabetes first diagnosed in pregnancy (DIP) and gestational diabetes (GDM), has significant adverse effects on pregnancy outcomes (including higher rates of large for gestational age and primary caesarean section)[3] and longer term risk for the offspring (obesity and diabetes)[4]. Importantly, gestational diabetes management, including that to achieve tighter glucose levels in pregnancy can lead to improved outcomes[5].

The Northern Territory (NT) has the highest proportion of Indigenous people in Australia, with 33% of the 3,904 NT births in 2014 to Indigenous mothers, of whom 62% lived in remote regions[6]. Indigenous mothers experience high rates of hyperglycaemia in pregnancy: 16% GDM and 4% pre-existing diabetes compared to 12% and less than 1%, respectively, in non-Indigenous NT women[6]. Perinatal outcomes are poorer for Indigenous than non-Indigenous mothers (20.5 and 9.1 deaths per 1000 births for Indigenous and non-Indigenous women respectively)[6]. In this context, the NT Diabetes in Pregnancy Clinical Register was established in 2011 to provide accurate epidemiological data for women with hyperglycaemia in pregnancy and to support quality improvement.

Although use of metformin in pregnancy is not currently endorsed by many international clinical guidelines, use has increased recently following key publications[7, 8]. The NT Clinical Register provides an excellent opportunity to assess outcomes associated with metformin use in a real-world setting. Both relatively high rates of metformin use and higher rates of adverse perinatal outcomes

among Indigenous women, may contribute to greater power to address this knowledge gap. We aimed to assess birth outcomes with metformin use, in both Indigenous and non-Indigenous women with GDM and type 2 diabetes, as there are limited real-world data on metformin use, including in high-risk pregnancies.

Material and Methods

Participants

The NT Diabetes in Pregnancy Clinical Register sits within the NT Diabetes in Pregnancy Partnership, thus operates as a partnership between the NT Department of Health, Aboriginal Medical Services Alliance of NT, Healthy Living NT, Baker Heart and Diabetes Institute and Menzies School of Health Research. All women residing in the NT with any type of hyperglycaemia in pregnancy (type 1 diabetes mellitus [T1DM], type 2 diabetes, DIP or GDM) are eligible for inclusion on the register. The DIP group were women with likely type 2 diabetes first identified in pregnancy.

Diagnostic criteria of GDM, DIP and pre-existing type 2 diabetes in pregnancy

The GDM diagnostic criteria changed during the course of the study, with a gradual increase in implementation of new guidelines throughout the NT between 2012 and 2014. Hence, women with GDM were diagnosed by either the 1998 Australian Diabetes in Pregnancy Society (ADIPS) guidelines[9] or a universal 75 g OGTT and revised glucose cut-points as recommended by the International Association of the Diabetes and Pregnancy Study Groups (IADPSG)[10] and the World Health Organisation (WHO)[11]. The ADIPS guidelines involved a two-step process (50gm glucose challenge test then two-point 75 g OGTT) and diagnosis on 75 g OGTT if fasting glucose 5.5 - 6.9 mmol/L or 2 hour glucose 8.0 – 11.0 mmol/L, whereas the WHO criteria are universal three-point 75 g OGTT with fasting glucose 5.1 – 6.9 mmol/L or 1 hour glucose ≥ 10.0 mmol/L or 2 hour glucose 8.5 – 11.0 mmol/L. Among women with GDM diagnosed by OGTT, 77.4% met the

diagnostic criteria for both the ADIPS and WHO criteria, 102 (8.0%) women met ADIPS criteria alone and 186 (14.6%) women met WHO diagnostic criteria only. DIP was defined as fasting plasma glucose ≥ 7.0 mmol/L, or 2-hour plasma glucose ≥ 11.1 mmol/L, or HbA1c ≥ 6.5%[11]. Pre-existing type 2 diabetes in pregnancy was defined as documentation in medical records of type 2 diabetes prior to pregnancy.

Referral to the Clinical Register

Any health professional involved in the care of a woman with hyperglycaemia in pregnancy may refer to the register using a standard template. Referring practitioners include; general practitioners, aboriginal health practitioners, diabetes educators, medical specialists, nurses, midwives and dieticians. To promote the register, awareness was raised at local workshops, clinical meetings and websites targeting those working with pregnant women in the NT[12].

Consent to be on the register is obtained verbally and confirmed by a tick-box on the practitioner's referral form. Those under the age of 16 require additional verbal consent from a parent or guardian. All patients are provided with a written fact sheet including details on requesting removal from the register. Data are collected by those involved in the care of women with hyperglycaemia in pregnancy (such as remote area midwives, physicians and diabetes educators) as well as the clinical register staff. Variables are collected at two time points (at time of referral to register and after birth). The study was approved by the Human Research Ethics Committee (HREC) of the NT Department of Health and Menzies School of Health Research and Central Australian HREC.

Coverage of the clinical register

The coverage of the register was assessed by comparing the clinical register with the Midwives' Data Collection (MDC), a population-based continuous census of all births that occur in the NT (including in hospitals, communities and non-hospital births). The MDC records the presence of

pre-existing diabetes and GDM[13]. Using this method, the estimated coverage of the clinical register was 44.6% in 2012 (n=205 compared to n=460[13]), 69.6% in 2013 (n=371, n=533[14]) and 77% in 2014 (n=453, n=587)[6]. Data from 2015 onwards are not yet available. Notably, rates of coverage for Indigenous and non-Indigenous women with type 2 diabetes were 100% in 2014[12].

Perinatal data and outcome definitions

Baseline variables collected at the time of referral to the register include: maternal age, ethnicity, location of residence, diabetes type, body mass index (BMI, using first available weight in pregnancy collected from medical records), presence of hypertension, smoking or alcohol use, gestational age and results of oral glucose tolerance test (OGTT) or glycated haemoglobin [$HbA1_C$]. Note that there are no OGTT data for women with pre-existing type 2 diabetes (as per clinical guidelines this test was not performed) and similarly no HbA1c data for women with GDM. Gestational age at first visit was defined as the minimum/earlier of either the gestational age at first haemoglobin measurement (routinely performed on first antenatal visit) or the gestational age at first ultrasound. This first visit was to any health professional eligible to refer to the register. Gestational age is presented in weeks (days were converted to a decimal fraction of a week). Variables collected following birth from medical records include: diabetes medication used in the third trimester, location and mode of delivery, gestational age, birth weight and birth complications. Birth weight z-score was adjusted for gender and gestational age at birth[15]. Large for gestational age (LGA) was birth weight >90th centile on gender-specific growth percentiles for Australian infants[15, 16]. Severe adverse events was a composite outcome defined as one of: death (maternal, stillbirth and neonatal death), delivery <32 weeks, prolonged hospitalisation with at least 5 days higher level neonatal care (neonatal intensive care or special care nursery), condition which results in significant disability/incapacity or requires medical intervention to prevent permanent damage[3].

Statistical methods

De-identified data from 1st January 2012 until 31st December 2016 were extracted from the register and analysed using STATA 15.0 (College Station, TX, USA). For the purpose of this analysis we excluded women with type 1 diabetes, those without information on metformin medication in the third trimester, and a pregnancy gestation of at least 20 weeks. Over the 5 years, 1786 pregnancies involving women with hyperglycaemia in pregnancy were referred to the clinical register (26 sets of twins). We excluded the following participants from analyses: 103 women without information on use of metformin in the third trimester, 27 women with type 1 diabetes, and 7 women whose pregnancy ended prior to 20 weeks gestation. Univariate associations between variables were determined using Pearson's chi-square test for categorical outcomes and Student's t-test for continuous outcomes. All univariate analyses were stratified by diabetes type (type 2 diabetes, DIP and GDM) and, within diabetes type, by Indigenous ethnicity. Multivariable linear regression models for continuous outcomes and multivariable logistic models for dichotomous outcomes were used to assess the association between metformin and each outcome after adjusting for the potential confounding effect of age, body mass index (BMI), insulin medication and, when appropriate, parity. In multivariable regression, for statistical power reasons, DIP and GDM were combined and analyses were stratified by diabetes type (type 2 diabetes and DIP/GDM) and, within diabetes type, by Indigenous ethnicity.

Results

Of 1649 pregnancies (from 1505 women, with 1675 babies), 73.2% were women with GDM, 10.3% DIP and 16.5% type 2 diabetes, with rates differing by ethnicity as follows: Indigenous women, 57.7% GDM, 13.5% DIP, 28.8% type 2 diabetes; non-Indigenous women 88.4% GDM, 7.1% DIP and 4.5% type 2 diabetes. Indigenous women represented 39% of those with GDM, 65% (n=110) of those with DIP, and 86% (n=234) of those with type 2 diabetes.

Among women with type 2 diabetes (Table 1), characteristics were similar for women managed with and without metformin (except for higher age and parity among women using, compared to not using metformin), although findings are limited by small numbers of women with type 2 diabetes not treated with metformin. Data were available for 131 women with type 2 diabetes regarding metformin use prior to the third trimester [on referral to the register, mean (sd) gestational age 16.6 (6.5) weeks]: 109 (83%) women were using metformin at that time. Among those with DIP and among those with GDM (Table 1), differences within both non-Indigenous and Indigenous groups were evident for those using metformin (compared to without metformin) as follows: higher BMI, earlier gestational age at OGTT, and higher use of insulin in third trimester.

A higher proportion of Indigenous women were prescribed metformin compared to non-Indigenous women (Supplemental Figure), particularly striking in 2012 (56% Indigenous vs 14% non-Indigenous women with GDM/DIP). Rates of metformin use were high in type 2 diabetes for both Indigenous and non-Indigenous women in 2016 (90% and 100% respectively). Over time (2012-2016) there was an increase in metformin use among non-Indigenous women with type 2 diabetes (43% to 100%) and GDM/DIP (14% to 35%). As expected, insulin was prescribed more commonly in type 2 diabetes compared to GDM. There were no significant differences in insulin rates between Indigenous and non-Indigenous women with GDM.

There were higher rates of poor birth outcomes for women with type 2 diabetes compared to DIP and GDM (Table 2). On unadjusted analysis (Table 3), metformin use was associated with shorter gestation (37.7 weeks with metformin vs 38.5 weeks without metformin in Indigenous mothers with GDM/DIP). After adjusting for age, BMI, parity and insulin use, metformin was associated with a shorter gestational age among Indigenous and non-Indigenous women with GDM/DIP. A similar trend was seen in the proportion of pre-term births (<37 weeks, among Indigenous women with GDM/DIP) in those prescribed metformin, however this did not reach statistical significance on

multivariate analysis. There were no differences in other key perinatal outcomes between groups with and without metformin use. The effect of metformin was minimally or not at all confounded by any of the statistically significant covariates in the multivariable models. Results were unchanged in a sensitivity analysis involving the 815 women who participated in a sub-study that collected data on induction of labour[17]: gestational age remained independently earlier in the metformin group after adjustment for induction. However, in a sensitivity analysis excluding women managed with medical nutrition therapy alone (thus comparing women managed with metformin, with or without insulin, to women managed with insulin alone, Table 3), there was no significant difference in gestational age at birth (nor prematurity) between those using metformin compared to those using insulin alone. On a secondary analysis including gestational age at recorded BMI in the model where available, this variable was not associated with any of the outcomes and never a confounder for BMI. Among the group of women with GDM, results were unchanged on analysis involving only the women with GDM diagnosed by WHO criteria (excluding the 102 women diagnosed by ADIPS criteria only and who were normal according to the WHO criteria).

Discussion

We report, from the first five years of the NT Diabetes in Pregnancy Clinical Register, that use of metformin was relatively high and has increased over time in non-Indigenous women with type 2 diabetes and GDM. We observed no clear evidence of any adverse outcomes related to the use of metformin for the treatment of hyperglycaemia in pregnancy. Although we observed an earlier gestational age with metformin use in this real-world study, it did not remain after exclusion of women managed by medical nutrition therapy alone..

The epidemic of type 2 diabetes in indigenous peoples[1] is clearly evident from the clinical register, with a third of Indigenous mothers with hyperglycaemia in pregnancy having pre-existing type 2 diabetes, and nearly half of Indigenous mothers having either pre-existing or likely newly diagnosed type 2 diabetes. This is consistent with the very high rates of type 2 diabetes in Indigenous women[1]. Optimising glycaemia in women with pre-existing diabetes in pregnancy contributes to improved outcomes, thus it is a clinical priority to improve care for these women and potentially influence the metabolic health of mother and child lifelong.

Recommendations regarding metformin use in pregnancy vary widely, partly as its ability to cross the placenta has raised concern, as has the lack of long-term follow-up data[18-22]. Recent randomised controlled trials have reported comparable outcomes to insulin therapy in GDM[7], and a clinical trial in type 2 diabetes in pregnancy reported metformin to be safe and effective[8]. A meta-analysis reported lower gestational weight gain and lower risk of pre-eclampsia among women with GDM treatment with metformin compared to insulin[23]. Despite this, metformin use in pregnancy is not currently endorsed by Australian regulatory authorities or professional bodies. Previous guidelines by the Australasian Diabetes in Pregnancy Society recommend that metformin is not for routine use in pregnancy, although its use may be warranted in some situations, after detailed discussion with the woman regarding risks and benefits[18]. However, more recently metformin is used in many Australian institutions[24], is included in the UK NICE Guidelines as an option in GDM and type 2 diabetes in pregnancy[25], and advice by the American Diabetes Association is that insulin is the preferred medication but that metformin may be used[26]. Local Indigenous health guidelines suggest continuing metformin if a woman is already using it and considering commencement if insulin is not a feasible option and after discussion with the woman regarding risks and benefits[27]. Rates of metformin use in our clinical register are high, particularly among Indigenous women, while for non-Indigenous women metformin use increased over the five years. This clinical practice reflects use of both local guidelines and contextual challenges of remote Indigenous health, including

poverty, food insecurity, high health staff turnover and limited specialist support. It is interesting that metformin use among non-Indigenous women increased considerably over the study period, a group that generally does not experience the above contextual challenges. It is possible that the increased use among non-Indigenous women may relate to increasing health provider familiarity with metformin and/or inclusion of metformin in UK NICE Guidelines in 2015[25], and/or tailoring of medication selection by clinicians according to individual patient characteristics/phenotype[28], however further work is needed to explore the reasons.

Acknowledging the limitations of a non-randomised observational prospective cohort, we noted no difference in clinically significant adverse birth outcomes in women treated with metformin. The slightly earlier gestational age in women with GDM and DIP taking metformin did not remain independently significant after exclusion of women on medical nutrition therapy alone and thus may not be of clinical significance. Although there was a trend in higher rates of births < 37 weeks among Indigenous women with GDM/DIP, the difference was not statistically significant on multivariable analysis. A higher rate of prematurity was reported in the Metformin in GDM trial[7] but this finding has not been consistently replicated in other studies[29], and the mechanisms of the observed findings are not known[30]. The observed earlier gestational age at delivery among women taking metformin (when women on medical nutrition therapy alone were included in the comparison group with women on insulin alone) may relate to interventions such as induction, however a sensitivity analysis involving the 815 women who participated in a sub-study that collected data on induction of labour did not alter the outcome: gestational age remained independently earlier in the metformin group after adjustment for induction. We also observed a higher mean birth weight z-score in non-Indigenous women with type 2 diabetes and Indigenous women with GDM who used metformin. As this finding was not seen consistently across all groups, its significance is uncertain. A large randomised trial comparing metformin to insulin therapy showed no difference in birth weights between those treated with metformin compared to insulin[7].

The clinical register has provided important epidemiological data in a high-risk population experiencing contextual challenges of socio-economic disadvantage and remoteness. However, there are some limitations to its interpretation. The data are not a complete record of all women with hyperglycaemia in pregnancy in the NT and it is not possible to ascertain which subgroups are under-reported thus influencing interpretation of the data. Our study is limited by no data on: duration of metformin use prior to the third trimester, pre-conception maternal weight, gestational weight gain, previous caesarean section, adherence to therapy, side effect profile and level of glycaemic control achieved during pregnancy. There were small numbers of women in some groups (such as non-Indigenous women with type 2 diabetes, and women with type 2 diabetes not using metformin), thus with limited sample size, signals of modest effect size may have been missed. Finally, a key limitation is that this is an observational cohort thus we are unable to assess causality and it is difficult to assess the impact of key confounding variables on outcomes. In particular, we were not able to adjust for factors that influenced the clinical decision to use metformin or insulin. It is notable that rates of risk factors such as smoking and obesity were higher among Indigenous than non-Indigenous women. Although these variables are included in adjusted models, other unmeasured variables may have contributed to our findings, including clinicians' decisions to induce women pre-term who they perceived to be at high-risk.

A key strength of the NT Diabetes in Pregnancy Clinical Register is that it sits within the NT Diabetes in Pregnancy Partnership, a partnership between health service providers, policy makers and researchers. Clinical register data thus provide valuable quality improvement data that have been and will continue to be used to inform design of models of care interventions in order to improve outcomes for women with hyperglycaemia in pregnancy and their babies. As we have recently reported, it is important that a clinical register is developed alongside other efforts to

improve health systems, rather than in isolation, in order to optimise benefits for patients, clinicians and health services[12, 31].

In conclusion, we report relatively high rates of metformin use among Indigenous women with GDM and type 2 diabetes in pregnancy, with increasing usage among non-Indigenous women with GDM and type 2 diabetes. We found no clear evidence of any adverse outcomes related to the use of metformin for the treatment of hyperglycaemia in pregnancy. . Although limited by its observational design, the clinical register provides valuable data that inform models of care changes to improve outcomes for women and their babies, particularly among the high-risk Indigenous Australian population.

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Disclosure: All authors have nil competing interests to declare.

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Figure Legend

Supplemental Figure: Use of diabetes medication in third trimester

Panel A: Percent of women prescribed metformin in third trimester

Panel B: Percent of women prescribed insulin in third trimester

Table 1: Characteristics of 1649 pregnancies from mothers on the NT Diabetes in Pregnancy Clinical Register, by use of metformin in the third trimester

	T2DM				DIP				GDM			
	Non-indigenous women		Indigenous women		Non-indigenous women		Indigenous women		Non-indigenous women		Indigenous women	
	No metformin	Metformin use	No metformin	Metformin use	No metformin	Metformin use	No metformin	Metformin use	No metformin	Metformin use	No metformin	Metformin use
	n=12	n=26	n=25	n=209	n=35	n=24	n=35	n=75	n=547	n=191	n=265	=205
Age (years)	30 (6.7)	35.4 (3.9)**	29.1 (7.0)	31.1 (5.7)	32.4 (4.6)	31.0 (6.3)	28.2 (7.4)	29.2 (6.1)	31.6 (4.9)	31.7 (5.0)	28.0 (5.9)	29.0 (6.6)
BMI (kg/m^2)	30.9 (8.6)	30.5 (6.9)	31.7 (5.3)	31.5 (5.8)	27.3 (3.8)	28.5 (6.1)	29.9 (8.3)	30.9 (6.2)	27.1 (5.8)	29.7 (7.1) ‡	28.0 (7.3)	29.5 (7.2)*
GA at first weight	14.5 [13.4,20.6]	12.0 [9.7,16]	13.3 [7.9,19.3]	12.1 [7.7,20]	17.5 [14.3,21.9]	16.4 [13.7,18.9]	17.3 [9.6,28.9]	18.9 [9.4,27.5]	14.7 [12.7,17.6]	14.4 [13.3,17.6]	17.4 [10.7,23.4]	15.3 [8.4,25.9]**
Smoking†	0 (0)	1 (3.9)	12 (50.0)	90 (43.1)	0 (0)	2(8.3)	16 (45.7)	34 (46.0)	28 (5.2)	13 (6.8)	115 (43.4)	88 (43.1)
Nulliparity†	6 (50)	8 (30.8)	8 (32.0)	28 (13.4)*	18 (51.4)	8 (33.3)	12 (34.3)	15 (20.0)*	342 (44.3)	85 (44.5)	71 (26.8)	41 (20.0)
Insulin use 3rd trim†	11 (92.0)	20 (76.9)	18 (72.0)	163 (78.0)	16 (45.7)	17 (70.8)	11 (31.4)	43 (57.3)*	156 (28.5)	81 (42.4) ‡	33 (12.5)	69 (33.7) ‡
OGTT < 20 weeks†					1 (2.9)	6 (25.0)*	6 (18.2)	19 (27.5)	47 (8.9)	47 (25.7) ‡	26 (10.3)	66 (33.7) ‡
GA (wks) at OGTT					27.4 (3.4)	23.0 (7.9)**	27.4 (7.7)	24.0 (8.2)*	26.7 (4.8)	23.8 (7.6) ‡	26.9 (5.7)	22.4 (8.1) ‡
Fasting glucose (mmol/L)					6.4 (2.7)	6.1 (1.2)	5.9 (1.7)	6.5 (1.9)	4.6 (0.6)	4.9 (0.5) ‡	4.7 (0.8)	4.9 (0.7)*
1h glucose (mmol/L)					10.0 (3.0)	12.1 (2.6)**	10.0 (2.6)	12.3 (2.4)**	9.7 (1.6)	9.8 (1.7)	9.4 (1.7)	9.7 (1.9)
2hr glucose (mmol/L)					10.4 (2.5)	11.6 (2.2)	10.2 (2.9)	11.7 (2.9)*	8.5 (1.2)	8.2 (1.5)*	8.1 (1.6)	8.3 (1.6)
GA (wks) at HbA1c	11.9 [6.1,15.1]	7.9 [5.6,10.1]	10.6 [6,17.4]	8.7 [5.7,16.3]	33.3 [29.1,36.1]	29* [18.1,34.1]	31.1 [19.4,36]	27.6 [12.1,33.7]	33.3 [28,35.9]	30.4 [24,34] ‡	27.9 [14.8,33.7]	23.1 [9,32.9]*
HbA1c (%)	6.5 (1.5)	6.6 (1.5)	8.2 (2.2)	7.9 (2.0)	5.9 (0.47)	5.9 (0.8)	6.1 (0.72)	6.5 (0.95)	5.4 (0.46)	5.4 (0.37)	5.4 (0.38)	5.6 (0.41) **
HbA1c (mmol/mol)	48.7 (16.5)	48.4 (16.2)	66.3 (23.0)	63.3 (21.7)	41.0 (5.2)	41.5 (8.8)	43.0 (7.9)	47.2 (10.4)	35.8 (5.0)	36.0 (4.1)	36.0 (4.2)	37.5 (4.4)
GA at refferal	20.6 [15,33.6]	17.4 [11,33.3]	23.2 [11.7,30.1]	31.1 [21.7,36]	33.7 [30.7,37.3]	33.4 [30,36.4]	36.9 [33.1,37.9]	34 [30.4,36.3] **	34 [31.1,36.9]	31.8 [28.1,34.9] ‡	36.6 [33.4,18.1]	35.6 [30,37.4] ‡
GA (wks) at first visit	6.9 [5.9,9.5]	7.2 [6,8.6]	7.3 [5.9,13.1]	8.7 [6.3,14.3]	7.1 [6.1,9.4]	6.9 [5,9.2]	10.1 [7.6,21.7]	9.7 [6.9,18.7]	6.9 [5.6,9.1]	6.6 [5.5,8.7]	10.3 [7,17]	8.1 [6.3, 13.4]

Data are mean (standard deviation), median [IQR] for GA at HbA1c or †number (percentage). * <0.05; **<0.01; ‡ <0.001: p value for differences between metformin groups within each ethnicity and diabetes type determined using Person's chi-square test for categorical outcomes and Student's t-test for continuous outcomes. BMI, body mass index; GA, gestational age; OGTT, oral glucose tolerance test; Hb, haemoglobin

The sample size was smaller for the following characteristics in each group respectively as follows: BMI, n=12, 25; 23, 198; 34, 24; 34, 72; 533,190; 256,194;
GA at 1st weight, n= 10, 22; 21,162; 26,20; 24,56; 440,157; 179,153;
GA at OGTT/any glucose measure(not not all three measures of fasting, 1 hour or 2 hour glucose were available for all participants, n/a: not applicable for women with T2DM), n= n/a, n/a; n/a, n/a; 35,24; 33,69; 528,183;252,195;
Fasting glucose, n= n/a, n/a; n/a, n/a; 35,24; 32,68; 528, 183; 249, 193; 1h glucose, n= n/a, n/a; n/a, n/a; 31,24; 27,58; 486;173;217,165; 2hr glucose, n= n/a, n/a; n/a, n/a; 35,24; 33,69; 527,182; 248, 195;
Ga at HbA1c, n= 11, 25; 31,193; 19,17; 26,67; 223,124; 160,169;
HbA1c, n= 12,26; 24,202; 20,18; 27,70; 230,127; 163,170.

Table 2: Birth outcomes of 1649 pregnancies (1675 babies) from mothers on the NT Diabetes in Pregnancy Clinical Register, by use of metformin in the third trimester

	T2DM				DIP				GDM			
	Non-indigenous women		Indigenous women		Non-indigenous women		Indigenous women		Non-indigenous women		Indigenous women	
	No metformin	Metformin use	No metformin	Metformin use	No metformin	Metformin use	No metformin	Metformin use	No metformin	Metformin use	No metformin	Metformin use
	n=13	*n=27*	*n=25*	*n=210*	*n=36*	*n=24*	*n=36*	*n=75*	*n=557*	*n=192*	*n=272*	*n=208*
Admission to higher neonatal care	7 (58.3)	11 (42.3)	15 (71.4)	136 (66.0)	12 (33.3)	9 (39.1)	10 (28.6)	32 (42.7)	137 (25.0)	43 (23.1)	87 (32.5)	80 (38.5)
Serious adverse events	3 (25)	5 (19.2)	6 (28.6)	53 (26.4)	3 (8.3)	2 (9.1)	3 (8.6)	11 (14.7)	27 (4.9)	11 (5.8)	15 (5.6)	15 (7.4)
	n=11	*n=25*	*n=25*	*n=208*	*n=34*	*n=24*	*n=34*	*n=75*	*n=537*	*n=190*	*n=258*	*n=202*
Gestational age	37.7 (1.6)	38.2 (1.1)	37.0 (1.7)	37 (2.1)	38.6 (1.6)	38.1 (1.8)	38.7 (1.1)	37.9 (1.4)**	38.7 (1.5)	38.4 (1.6)**	38.5 (1.9)	37.6 (2.1) ‡
Birth weight z-score	-0.09 (1.92)	0.60 (1.29)	1.44 (2.0)	0.90 (1.49)	-0.22 (0.18)	0.38 (1.42)	0.65 (1.24)	0.86 (1.61)	-0.03 (1.01)	-0.03 (0.99)	-0.13 (1.12)	0.30 (1.27) ‡
GA < 37 weeks	2 (20)	4 (17.4)	9 (42.9)	71 (35.5)	2 (5.9)	3 (13)	2 (5.6)	11 (14.7)	41 (7.8)	17 (9.0)	24 (9.3)	34 (16.8)*
Caesarean section	5 (50)	9 (39.1)	16 (76.2)	135 (67.5)	11 (32.4)	11 (47.8)	12 (35.3)	43 (57.3)*	204 (38.7)	86 (45.7)	101 (39.2)	97 (48.0)
SGA	5 (50.0)	0 (0)***	1 (4.8)	13 (6.5)	6 (17.7)	2 (8.7)	1 (2.9)	6 (8.1)	50 (9.5)	20 (10.7)	33 (12.8)	17 (8.4)
LGA	3 (30.0)	5 (22.0)	11 (52.4)	75 (37.5)	3 (8.8)	5 (21.7)	10 (29.4)	27 (36.0)	53 (10.1)	19 (10.1)	29 (11.2)	39 (19.3)*

Note that n differs for various outcomes as follows: serious adverse events and admission to higher level neonatal care, n=1675; Gestational age at birth, birth weight Z score, LGA, SGA, caesarean section, 26 twin sets are excluded, n = 1623

* <0.05; **<0.01; ‡ <0.001: p value for differences between metformin groups within each ethnicity and diabetes type determined using Person's chi-square test for categorical outcomes and Student's t-test for continuous outcomes. BMI, body mass index; GA, gestational age; OGTT, oral glucose tolerance test; Hb, haemoglobin.

On comparisons by diabetes type without stratification by ethnicity and metformin, women with T2DM had higher rates of poor birth outcomes compared to women with DIP and GDM (all pairwise comparisons p-values were < 0.001; only LGA rates did not differ between T2DM and DIP).

Table 3: Birth outcomes, metformin vs no metformin in the third trimester

Results for all women						
			Unadjusted outcomes		**Multivariate analysis**	**p-value**
			No metformin use	**Metformin use**	**Metformin v no metformin**	
			mean (SD) or median [IQR]	mean (SD) or median [IQR]	beta coefficient (CI)	
Gestational age (weeks)						
	T2DM	Non-Indigenous mothers	37.7 (1.6)	38.2 (1.1)	0.8 (-0.3, 1.8)	0.14
		Indigenous mothers	37.0 (1.7)	37.0 (2.1)	-0.14 (-1.15, 0.86)	0.78
	GDM/DIP	Non-Indigenous mothers	38.7 (1.5)	38.3 (1.7)	-0.3 (-0.5, - 0.04)	**0.022**
		Indigenous mothers	38.5 (1.8)	37.7 (1.9)	-0.7 (-1.0, -0.4)	**<0.001**
Birth weight z-score						
	T2DM	Non-Indigenous mothers	-0.86 [-1.53 , 1.79]	0.31 [-0.16 , 0.86]	1.2 (0.1, 2.3)	**0.037**
		Indigenous mothers	2.14 [-0.18 , 3.17]	0.76 [-0.31 , 1.97]	-0.5 (-1.2, 0.2)	0.15
	GDM/DIP	Non-Indigenous mothers	-0.10 [-0.72 , 0.55]	-0.09 [-0.6 , 0.65]	-0.1 (-0.2, 0.1)	0.45
		Indigenous mothers	-0.15 [-0.99 , 0.67]	0.29 [-0.52 , 1.24]	0.2 (0.03, 0.4)	**0.025**
			n (%)	n (%)	OR (CI)	
Gestational age <37 weeks						
	T2DM	Non-Indigenous mothers	2 (20)	4 (17.4)	0.87 (0.08, 9.15)	0.90
		Indigenous mothers	9 (42.9)	71 (35.5)	0.71 (0.27, 1.88)	0.49
	GDM/DIP	Non-Indigenous mothers	43 (7.7)	20 (9.4)	1.12 (0.63, 2.00)	0.69
		Indigenous mothers	26 (8.9)	45 (16.3)	1.68 (0.97, 2.92)	0.61
Caesarean section						
	T2DM	Non-Indigenous mothers	5 (50)	9 (39.1)	0.53 (0.1, 3.3)	0.50
		Indigenous mothers	16 (76.2)	135 (67.5)	0.64 (0.20,2.1)	0.46
	GDM/DIP	Non-Indigenous mothers	215 (38.3)	97 (46.0)	1.21 (0.87, 1.68)	0.26

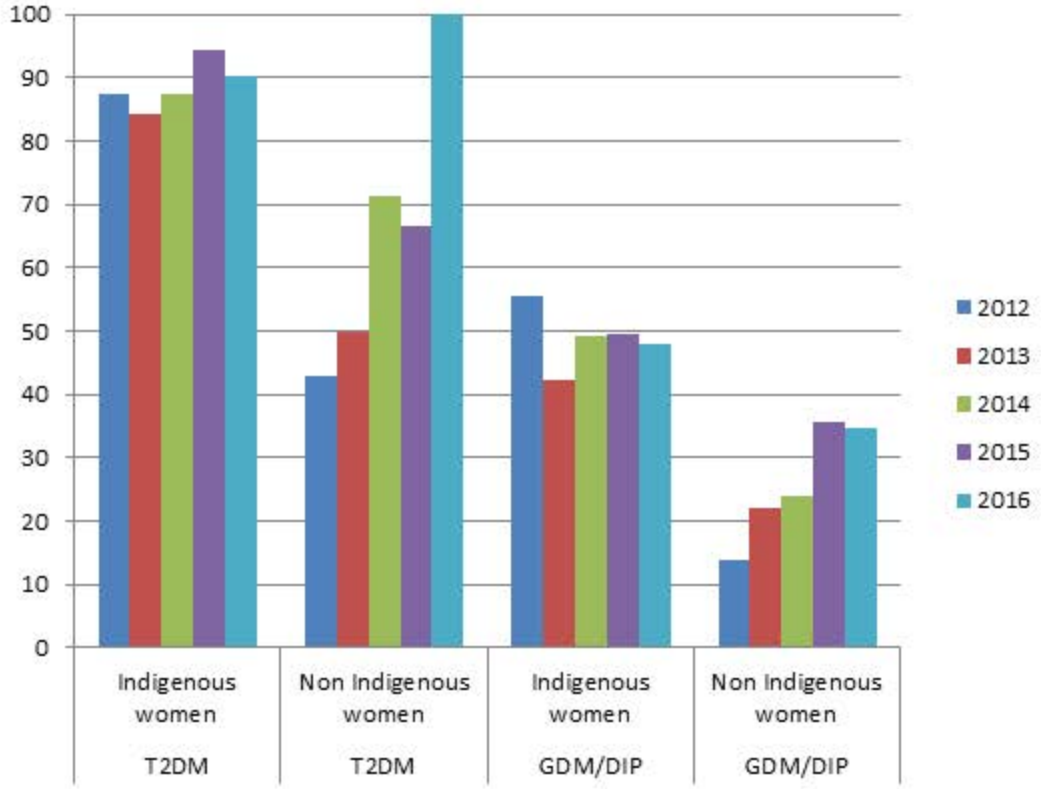
		Indigenous mothers	113 (38.7)	140 (50.5)	1.25 (0.87, 1.81)	0.22
Admission to special care nursery						
	T2DM	Non-Indigenous mothers	7 (58.3)	11 (42.3)	0.66 (0.14,3.14)	0.60
		Indigenous mothers	15 (71.4)	136 (66.0)	0.77 (0.26,2.25)	0.63
	GDM/DIP	Non-Indigenous mothers	149 (25.5)	52 (24.9)	0.83 (0.57,1.22)	0.35
		Indigenous mothers	97 (32.0)	112 (39.6)	1.14 (0.79,1.64)	0.50
Small for gestational age (SGA)						
	T2DM	Non-Indigenous mothers	5 (50.0)	0 (0.0)	N/A	
		Indigenous mothers	1 (4.7)	13 (6.5)	NA	
	GDM/DIP	Non-Indigenous mothers	56 (10.0)	22 (10.5)	1.13 (0.7, 1.9)	0.66
		Indigenous mothers	34 (11.7)	23 (8.3)	1.12 (0.6, 2.1)	0.71
Large for gestational age (LGA)						
	T2DM	Non-Indigenous mothers	3 (30.0)	5 (21.7)	NA	0.93
		Indigenous mothers	11 (52.4)	75 (37.5)	0.61 (0.2, 1.6)	0.33
	GDM/DIP	Non-Indigenous mothers	56 (9.8)	24 (11.4)	0.81 (0.5, 1.4)	0.45
		Indigenous mothers	39 (13.4)	66 (23.8)	1.5 (0.9, 2.5)	0.1
Serious adverse events						
	T2DM	Non-Indigenous mothers	3 (25)	5 (19.2)	N/A	
		Indigenous mothers	6 (28.6)	53 (26.4)	0.97 (0.35,2.71)	0.95
	GDM/DIP	Non-Indigenous mothers	30 (5.2)	13 (6.1)	1.01 (0.51,2.00)	0.98
		Indigenous mothers	18 (5.9)	26 (9.4)	1.32 (0.68,2.57)	0.42

Results of sensitivity analysis excluding women managed with medical nutrition therapy alone

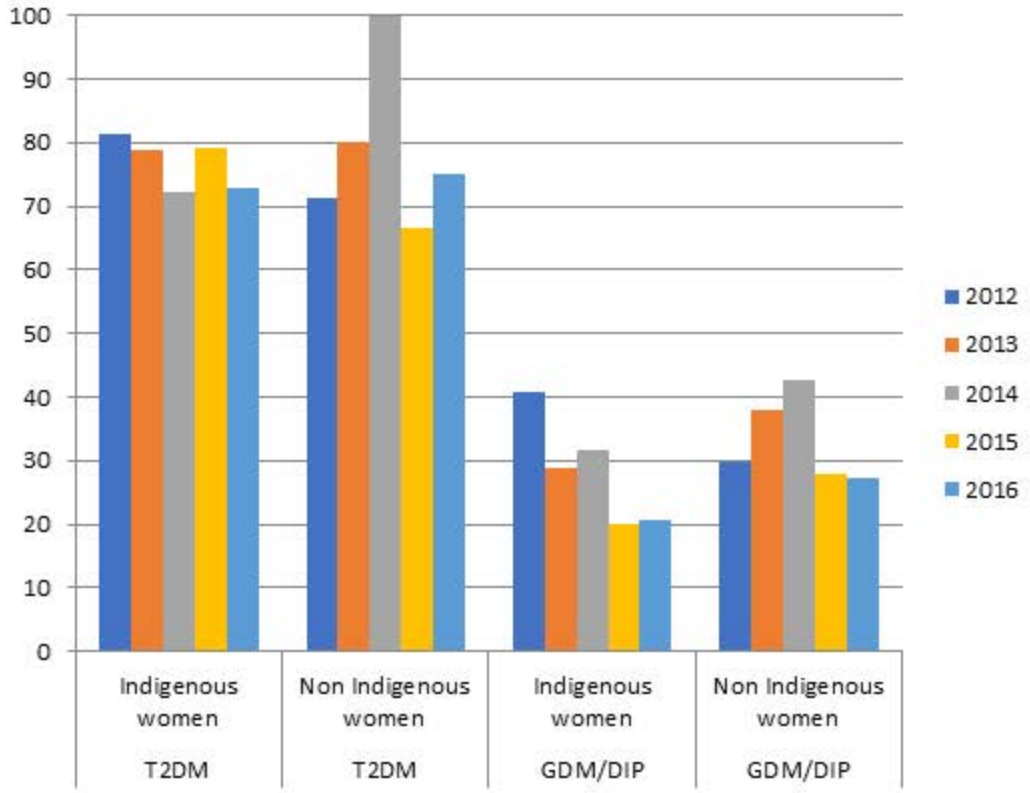
	Unadjusted outcomes		**Multivariate analysis**	**p-value**
	No metformin use	**Metformin use**	**Metformin v no metformin**	

			mean (SD) or median [IQR]	mean (SD) or median [IQR]	beta coefficient (CI)	
Gestational age (weeks)						
	T2DM	Non-Indigenous mothers	37.5 (1.6)	38.2 (1.0)	0.82 (-0.31,1.95)	0.15
		Indigenous mothers	36.6 (1.3)	36.9 (2.4)	-0.011 (-1.1,1.07)	0.98
	GDM/DIP	Non-Indigenous mothers	38.1 (1.9)	38.3 (1.7)	-0.039 (-0.44,0.37)	0.85
		Indigenous mothers	38.1 (1.5)	37.7 (1.9)	-0.55 (-1.18,0.09)	0.091
Birth weight z-score						
	T2DM	Non-Indigenous mothers	-1.28 [-1.53,1.79]	0.21 [-1.64,0.85]	1.24 (0.05,2.43)	**0.042**
		Indigenous mothers	2.39 [0.55,3.20]	0.81 [-0.29,2.0]	-0.59 (-1.33,0.17)	0.13
	GDM/DIP	Non-Indigenous mothers	0.22 [-0.53,0.81]	-0.085 [-0.6,0.65]	-0.13 (-0.39,0.13)	0.34
		Indigenous mothers	0.66 [-0.26, 1.53]	0.29 [-0.52,1.24]	0.13 (-0.34,0.59)	0.59

Multivariable models were adjusted for: maternal age, BMI and use Insulin medication in the third trimester. Birth weight z-score was additionally adjusted for parity.



	T2DM						GDM/DIP					
Ref Year	Indigenous women			Non-Indigenous women			Indigenous women			Non-indigenous women		
	n	N	%	n	N	%	n	N	%	n	N	%
2012	28	32	87.5	3	7	42.9	30	54	55.6	13	93	14.0
2013	27	32	84.4	5	10	50.0	50	118	42.4	40	180	22.2
2014	49	56	87.5	5	7	71.4	75	152	49.3	49	204	24.0
2015	49	52	94.2	2	3	66.7	62	125	49.6	58	162	35.8
2016	56	62	90.3	11	11	100.0	63	131	48.1	55	158	34.8



	T2DM						GDM/DIP					
Ref Year	Indigenous women			Non-Indigenous women			Indigenous women			Non-indigenous women		
	n	N	%	n	N	%	n	N	%	n	N	%
2012	26	32	81.3	5	7	71.4	22	54	40.7	27	93	29.0
2013	26	32	81.3	8	10	80.0	34	118	28.8	68	180	37.8
2014	41	56	73.2	7	7	100.0	48	152	31.6	87	204	42.6
2015	42	52	80.8	2	3	66.7	25	125	20.0	45	162	27.8
2016	46	62	74.2	9	11	81.8	27	131	20.6	43	158	27.2