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Original Research

Implementation and Evaluation of the "Metformin First" Protocol for Management of Gestational Diabetes

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Key Messages

- Evidence now supports the safety and efficacy of metformin use for management of gestational diabetes mellitus (GDM).
- This is the first trial to evaluate a real-world clinical protocol that offers metformin as a first-line drug therapy for management of GDM.
- Introduction of the "Metformin First" protocol has resulted in no change to pregnancy outcomes and has improved patient satisfaction and clinic efficiency.

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ABSTRACT

Objectives: Although metformin has traditionally been avoided in pregnancy, evidence now supports its safety and efficacy for management of gestational diabetes mellitus (GDM). The primary objective of this study was to evaluate the clinical impact of a metformin-based approach for GDM management through assessment of pregnancy outcomes, clinic efficiency and patient satisfaction.
Methods: A retrospective chart review was conducted of new GDM patients seen before (January to July 2015) and after (January to September 2016) implementation of the "Metformin First" (MF) protocol. A prospective patient survey was also administered and responses were compared with a similar survey from 2013 (acting as a historical control).
Results: Of the 264 patients included in the chart review, 90 were seen in the pre-MF period and 174 in the post-MF period. There were no significant differences in rates of pregnancy complications (obstructed labour, infants born large for gestational age, neonatal intensive care unit admissions and infant hypoglycemia) between the 2 study periods. Blood glucose control was also comparable and satisfactory across both time periods. Of the 65 patients initially started on metformin, 18 (28%) required supplemental insulin therapy. Nonetheless, overall percentage of patients started on insulin dropped significantly (33% in 2015 vs 17% in 2016, p=0.003). Patient satisfaction scores at the clinic also increased following implementation of the MF protocol (4.68/5 in 2016 vs 4.3/5 in 2013, p=0.014).
Conclusions: Introduction of the MF protocol, which gave patients an informed choice between insulin and metformin, was associated with similar glycemic control and pregnancy outcomes, but improved patient satisfaction and clinic efficiency.

Mots clés:
diabète sucré gestationnel
metformine
soins périnatals
issues de la grossesse

RÉSUMÉ

Objectifs : Bien qu'on évite généralement d'employer la metformine durant la grossesse, des données probantes corroborent désormais son innocuité et son efficacité dans la prise en charge du diabète sucré

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gestationnel (DSG). L'objectif principal de la présente étude était d'évaluer les répercussions cliniques d'une approche axée sur la metformine lors de la prise en charge du DSG au moyen de l'évaluation des issues de la grossesse, de l'efficience clinique et de la satisfaction des patientes.
Méthodes : Nous avons mené une revue rétrospective des dossiers de nouvelles patientes atteintes du DSG vues avant (de janvier à juillet 2015) et après (de janvier à septembre 2016) la mise en œuvre du protocole de la « Metformine en première intention » (MPI). Nous avons également fait passer de manière prospective une enquête aux patientes et avons comparé leurs réponses à une enquête similaire de 2013 (qui sert d'enquête témoin historique).
Résultats : Parmi les 264 patientes considérées dans la revue des dossiers, 90 ont été vues dans la période pré-MPI et 174 dans la période post-MPI. Il n'y a eu aucune différence dans les taux de complications liées à la grossesse (travail obstrué, enfants de poids élevé pour l'âge gestationnel, admissions à l'unité de soins intensifs néonatals et hypoglycémie infantile) entre les 2 périodes étudiées. La régulation de la glycémie était également comparable et acceptable dans les deux périodes. Parmi les 65 patientes qui avaient commencé au début à prendre de la metformine, 18 (28 %) ont eu besoin de l'insulinothérapie en complément. Néanmoins, le pourcentage global des patientes qui avaient commencé à prendre l'insuline a chuté de manière significative (33 % en 2015 *vs* 17 % en 2016; p=0,003). Les scores de satisfaction des patientes de la clinique ont également augmenté après la mise en œuvre du protocole de la MPI (4,68/5 en 2016 *vs* 4,3/5 en 2013; p=0,014).
Conclusions : La mise en œuvre du protocole de la metformine, qui permet aux patientes de faire un choix éclairé entre l'insuline et la metformine, a été associée à une régulation de la glycémie et des issues de la grossesse similaires, mais à une plus grande satisfaction des patientes et à une meilleure efficience clinique.

Introduction

An estimated 2% to 9% of all pregnancies are complicated by gestational diabetes mellitus (GDM) (1). Although untreated GDM is associated with increased patient morbidity, appropriate management significantly improves maternal and infant health outcomes (2,3). Historically, the approach to management of GDM has involved nutritional modifications as a first-line intervention, followed by initiation of insulin therapy if glycemic targets are not achieved within 2 weeks (2). Unlike insulin, oral hypoglycemic agents cross the placenta and are cleared at an increased rate during pregnancy; consequently, they have traditionally been avoided in management of GDM (2).

In recent years, several independent research groups have begun to evaluate the use of oral hypoglycemic drugs in pregnancy. The emerging body of evidence supports the safety and efficacy of various oral agents in the management of GDM (4–6). Most notably, a large-scale randomized, controlled trial of 751 women with GDM demonstrated that metformin therapy was not associated with increased perinatal complications, when compared with insulin (4). Multiple independent meta-analyses have also concluded pregnancy outcomes to be similar or slightly better in patients treated with metformin (with or without insulin) (5–8). No associations were observed between the use of metformin and risk of neonatal hypoglycemia, increased birthweight, incidence of caesarean section or incidence of large-for-gestational-age babies (5). In light of these findings, multiple institutions, including Diabetes Canada, the National Institute for Health and Care Excellence and the American College of Obstetricians and Gynecologists, have released updated guidelines now recommending metformin as the primary drug therapy for GDM (9–11).

In the clinical setting, metformin offers many additional benefits when compared with insulin. It is less expensive, easier to administer, and has been shown to be better accepted by patients (7). Metformin can also be prescribed through a standardized prescription, whereas initiation of insulin therapy is a more resource-intensive process, requiring individualized patient training. Patients receiving metformin still require ongoing staff monitoring to ensure glycemic targets are met and to assess whether supplemental insulin therapy should be provided.

The primary objective of this study was to evaluate the clinical impact of a metformin-based approach for management of GDM, through assessment of pregnancy outcomes, clinic efficiency and patient satisfaction.

Methods

In January 2016, the "Metformin First" (MF) protocol (Figure 1) was implemented at the Diabetes in Pregnancy Clinic (DIP) at Sunnybrook Health Sciences Centre, in Toronto, Ontario, Canada. Metformin was offered as a first option to all patients requiring medication for management of GDM. To evaluate the impact of this protocol, a mixed-methods evaluation approach was applied, consisting of a retrospective chart review and an anonymous patient satisfaction survey. Ethics approval was obtained through the hospital research ethics committee and informed consent was obtained from all survey participants.

MF protocol

All new GDM patients referred to the DIP clinic were first initiated on a 1-week trial of nutritional intervention and daily self-monitoring of 4 blood glucose values: fasting and 2 hours after each meal. Pharmacotherapy was recommended to patients with unsatisfactory blood glucose (BG) control, based on home BG self-monitoring results, despite adherence to lifestyle modifications. Patients were informed of 2 options—metformin (target dose 2000 mg/d) or insulin—and provided a handout discussing potential risks and benefits of each (see Supplementary Appendix). In particular, it was stressed that metformin crosses the placenta while insulin does not. Patients were also informed that there is a lack of data on long-term outcomes after metformin use in pregnancy, although results from a 2-year follow-up study showed no reason for concern (12). If at least 3 fasting BG measurements were >6.5 mmol/L at the initial visit, simultaneous metformin and intermediate-acting insulin at bedtime was offered.

Self-monitored BG results were reviewed every 2 weeks, on average, until patients were discharged from the clinic at 37 to 38 weeks' gestational age. For women receiving metformin therapy, supplementary insulin was recommended if glycemic control was not satisfactory (3 or more fasting BG measurements >5.3 mmol/L, postprandial 2 hours >6.7 mmol/L or postprandial 1 hour >7.8 mmol/L in 1 week). Patients were monitored regularly and metformin was discontinued if there were intolerable side effects or pregnancy complications, such as fetal growth restriction. Metformin was also discontinued if patients experienced hypoglycemia between 2 and 4 hours postprandial, while at the same time requiring insulin to reach their 2-hour targets.

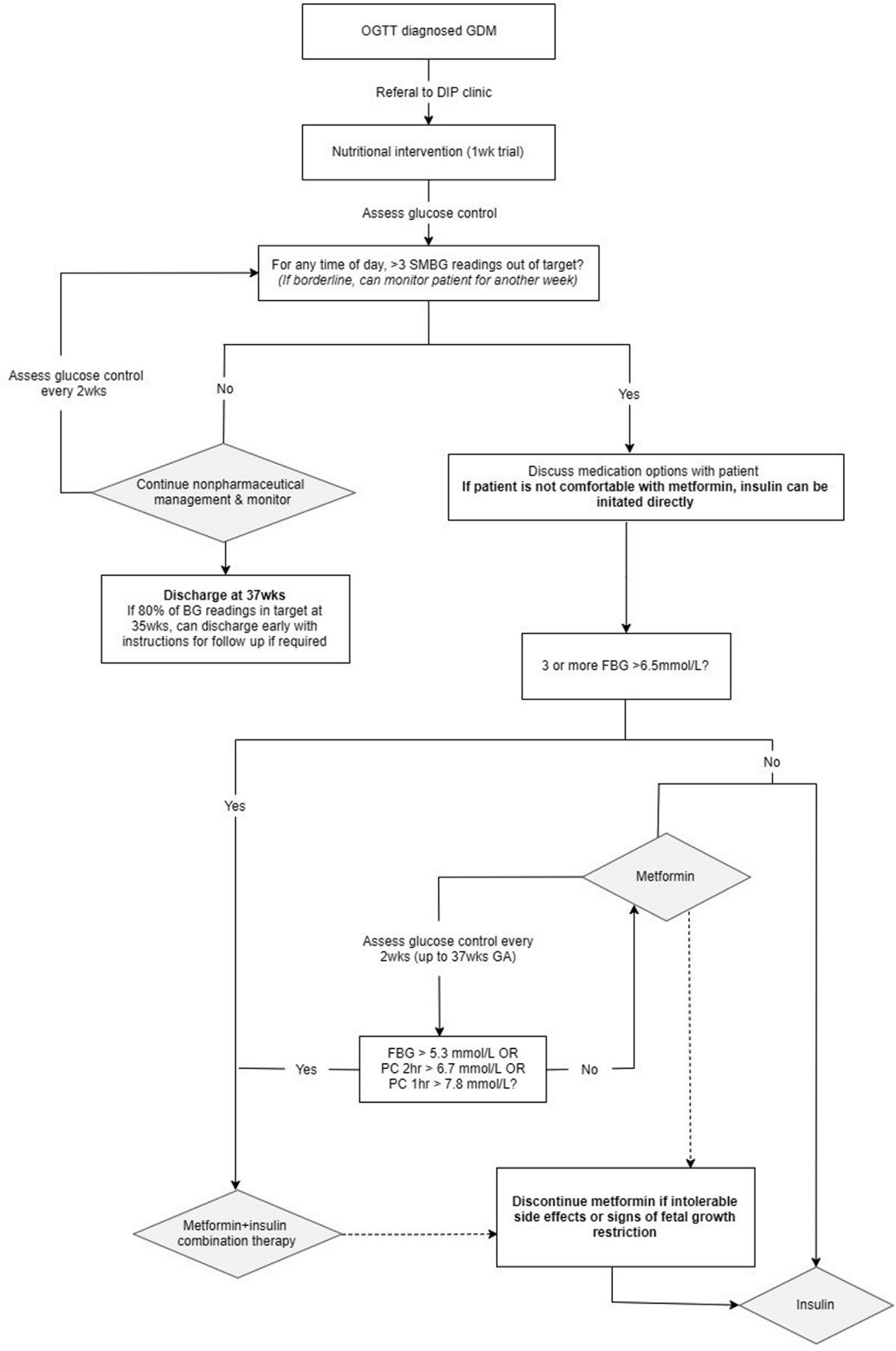

Figure 1. The "Metformin First" clinical decisionmaking algorithm. An overview is shown of the clinical criteria used to determine appropriate treatment regimens for patients. For patients requiring pharmaceutical therapy, the risks and benefits of both insulin and metformin are addressed. If patients are not comfortable using metformin, insulin therapy is initiated instead. *BG*, blood glucose; *FBG*, fasting blood glucose; *GA*, gestational age; *PC*, postprandial; *wks*, weeks.

Patient population and chart review methods

A retrospective chart review was conducted to extract data on patients seen at the clinic. All new GDM patients seen before introduction of the MF protocol (pre-MF period: January 2015 to June 2015) and after introduction of the protocol (post-MF period: January 2016 to September 2016) were included. Matching time-points were used to account for seasonal variation in patient volumes, and the second time period was extended to ensure an adequate proportion of patients reviewed were on metformin. Patients with any of the following conditions were excluded from the review: type 1 or type 2 pregestational diabetes, drug-induced GDM or a multiple-gestation pregnancy. Patients who delivered at a different institution, and patients for whom clinic data were not available were also excluded.

As retrospective chart review was used to assess all eligible patients, a priori power calculations were not conducted. Given that an average of 2 to 8 new GDM patients are seen weekly at the clinic, we estimated an expected sample size of 300 patients across the 2 study periods.

Relevant data points for all patients were extracted from the clinic's electronic medical record system, using a pre-established data collection form. Our primary outcomes of interest were pregnancy complications, including: obstructed labour, preterm delivery, infants born large for gestational age, infant hypoglycemia (BG <2.5 mmol/L) and admission to the neonatal intensive care unit (NICU). Large for gestational age was defined as a birthweight >90th percentile, and was calculated using values provided by the Health Canada Canadian Perinatal Surveillance System (13). Obstructed labour was defined by obstetrical documentation of shoulder/labour dystocia during delivery.

A secondary outcome of interest was BG control, which was determined using self-measured BG readings collected at the patient's last clinic visit. A mean percentage of "self-measured BG readings out of target" was calculated using the following formula:

$$\left(\frac{\#\text{ Out of target}_{\text{Fasting}} + \#\text{ Out of target}_{\text{PCB}} + \#\text{ Out of target}_{\text{PCL}} + \#\text{ Out of target}_{\text{PCD}}}{\text{Total \# of readings}}\right) \times 100$$

Data extracted from the chart review were also used to assess the proportion of patients started on insulin for the pre- and post-MF study periods.

Survey methods

To assess patient satisfaction with treatment regimen and quality of care received at the clinic, an anonymous survey was administered to patients before their last visit. The survey used for this study was developed by DIP clinic staff in 2013 as part of a quality improvement initiative. All patients seen at the DIP clinic for management of GDM were invited to participate and 40 surveys were collected in the summer of 2016. Responses were compared with results from 2013, before introduction of the MF protocol. The survey collected data on patient satisfaction score, patient-reported wait times and length of clinic visit.

Data analysis

All data analyses were carried out using SPSS version 20.0 (IBM Corp). Baseline statistics and outcomes of interest are reported using mean and standard deviation for continuous variables and as count and percent frequency for categorical variables. To identify any statistically significant differences ($p<0.05$) between the 2 study periods, chi-square analyses were conducted for categorical data and independent sample t tests for continuous data.

Results

Chart review

Participants: There were 320 new GDM patients seen at the clinic during the study. Fifty-six of these patients were excluded from the study due to lack of available clinic data (n=30) or ineligibility (n=26). Patients were excluded if they had type 1 or type 2 diabetes (n=9), drug-induced GDM (n=2), a multiple-gestation pregnancy (n=6) or if they delivered at a different institution (n=9). Of the remaining 264 patients included in the review, 90 were seen in the pre-MF period and 174 in the post-MF period.

Baseline maternal characteristics for these patients are summarized by study period in Table 1. Patients seen in the post-MF period were older (35.0 vs 33.9 years, p=0.04) and had higher parity (1.81 vs 1.56, p=0.02). Prepregnancy weight, weight at diagnosis and oral glucose tolerance test results were similar across both study periods.

Metformin profile: A total of 65 women were started on metformin during the post-MF study period (Figure 2). Of these patients, 42 (65%) were receiving the maximum metformin dose (1,000 mg twice daily) by their last clinic visit. Nine (14%) women experienced gastrointestinal side effects as a result of metformin use, although metformin was only discontinued and replaced with insulin in 2 patients. Eighteen (28%) patients started on metformin were provided supplemental insulin therapy over the course of their pregnancy.

The overall percentage of patients started on insulin dropped significantly after implementation of the MF protocol (33% in the pre-MF period vs 17% in the post-MF period, p=0.003). The percentage of patients treated with lifestyle measures alone also decreased during this time (68% vs 56%).

Table 1
Maternal baseline characteristics by study time period

	Pre-MF protocol (n=90)	Post-MF protocol (n=174)
Age, years*	33.9±4.1	35.0±4.3
Parity*	1.6±0.8	1.8±0.9
Prepregnancy weight, kg	68.5±20.9	69.4±17.3
Prepregnancy BMI	27.1±6.2	26.7±5.8
Weight at diagnosis, kg	78.3±17.5	80.1±18.0
GCT value	10.3±1.6	10.1±1.8
Fasting OGTT	4.9±0.8	4.9±0.8
One-hour OGTT	10.8±1.4	10.6±1.2
Two-hour OGTT	9.0±1.6	8.8±1.4
Treatment regimen, n (%)		
Lifestyle alone	61 (67.6)	98 (56.3)
Insulin	28 (31.1)	12 (6.9)
Metformin	0 (0.0)	46 (26.4)
Metformin + insulin	1 (1.1)†	18 (10.3)

BMI, body mass index; *GCT*, glucose challenge test; *MF*, "Metformin First"; *OGTT*, oral glucose challenge test.

* Independent sample t test shows significant difference at $p<0.05$ between study periods.

† Patient was on metformin for management of polycystic ovary syndrome and chose to continue medication during pregnancy.

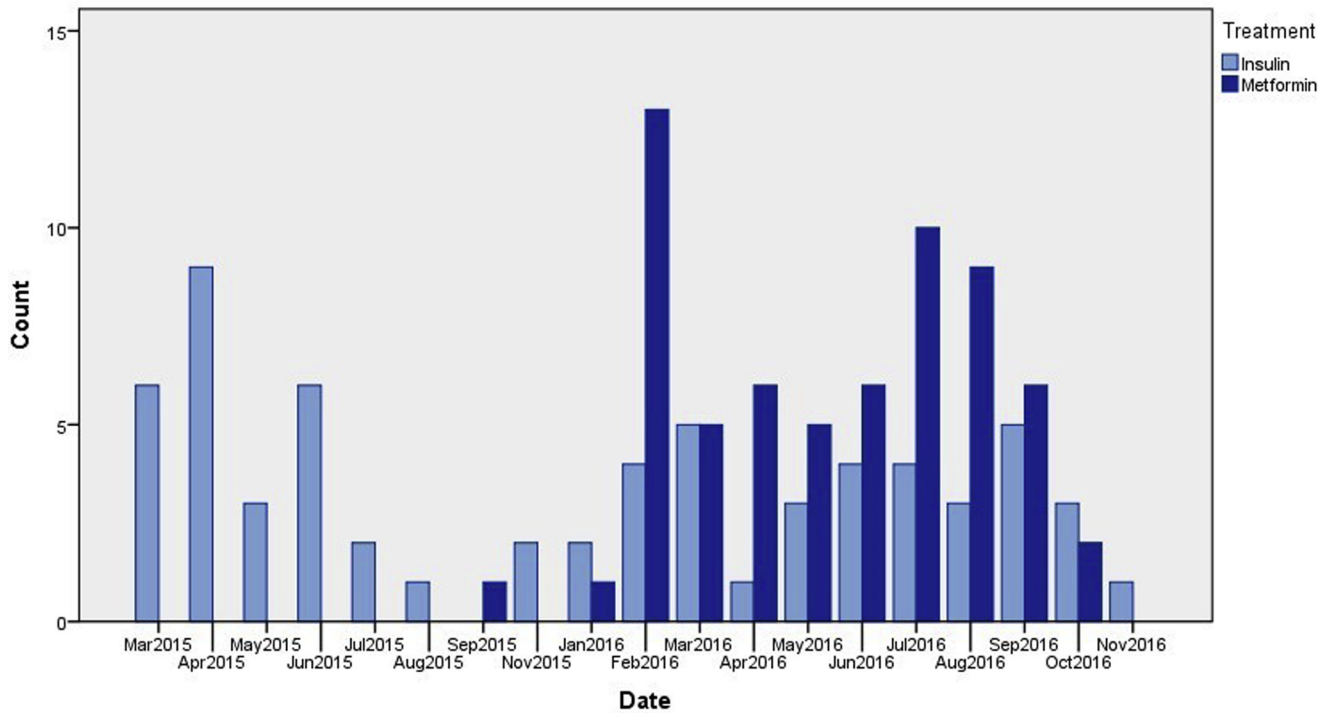

Figure 2. Distribution of patients started on insulin or metformin. The graph shows the number of patients started on insulin or metformin during the study period. After implementation of the "Metformin First" protocol in January 2016, the overall percentage of patients started on insulin dropped significantly (33% in 2015 vs 17% in 2016; p=0.003).

Outcomes: Blood glucose control: Blood glucose control was determined as the average percentage of self-measured blood glucose readings above target for each patient. The percentages of readings out of target were consistently low across the study sample (mean, 19.0±16.7%).

Pregnancy outcomes: Pregnancy outcomes of study participants are summarized in Table 2. Although labour outcomes were fairly consistent between the 2 time periods, there was a noted increase in the number of elective caesarian sections in the post-MF period (27% vs 12%, p=0.022). The overall incidence of neonatal complications was low in the study sample—there were 13 cases (incidence rate 4.9%) of obstructed labour, 30 cases of preterm delivery (11.4%), 20 infants (7.6%) who were born large for their gestational age, 16 cases (6.1%) of infant hypoglycemia and 18 cases (6.8%) of NICU admission. No statistically significant differences were observed in the rate of complications between the 2 study periods.

Patient survey results: Forty patient satisfaction surveys were collected at the clinic in the summer of 2016, after implementation of the MF protocol. When results were compared with survey responses from 2013 (used here as a historical control), a significant increase was seen in patient satisfaction scores (4.68±0.6 in 2016 vs 4.3±0.9 in 2013, p=0.014). No significant changes were observed in patient-reported times to be seen (22±20 minutes in 2016 vs 18±19 minutes in 2013) or length of clinic visits (30±25 minutes in 2016 vs 29±20 minutes in 2013).

Table 2
Clinical outcomes by study time period

	Pre-MF protocol	Post-MF protocol	p value
2.1 Blood glucose control, mean (SD)			
Self-measured BG readings out of target at last clinic visit (%)	18.7 (18.3)	19.8 (14.7)	0.183
2.2 Pregnancy outcomes, n (%)			
Labour outcomes			
Spontaneous vaginal	34 (37.8%)	53 (30.6%)	0.27
Induced labour	17 (18.9%)	22 (12.7%)	0.20
Elective caesarean section*	11 (12.2%)	47 (27.2%)	0.04†
Emergency caesarean section	20 (22.2%)	37 (21.4%)	0.87
Forceps/vacuum extraction	8 (8.9%)	15 (8.1%)	0.44
Pregnancy complications			
Preterm delivery	11 (12.2%)	19 (11.1%)	0.84
Obstructed labour	8 (8.9%)	5 (2.9%)	0.07
Infant born large for GA‡	5 (5.6%)	15 (8.6%)	0.47
Infant hypoglycemia	5 (5.6%)	11 (6.4%)	1.00
Admission to NICU	7 (7.8%)	11 (6.4%)	0.80

BG, Blood glucose; *GA*, gestational age; *MF*, "Metformin First"; *NICU*, neonatal intensive care unit..

* Independent sample t test results showing differences between study periods ($p<0.05$ considered significant).

† Statistically significant difference.

‡ Large for GA is defined as birthweight >90th percentile. The birthweight percentiles were calculated using values provided by Health Canada.

Discussion

Metformin use has traditionally been avoided during pregnancy, but our study adds to the evidence suggesting that it is a safe and effective pharmaceutical intervention for GDM. When comparing pregnancy outcomes at our clinic before and after implementation of the MF protocol, no significant changes were observed in rates of pregnancy complications, except for caesarean section rates. Although a significant increase was noted in the number of elective caesarean sections, this is likely an incidental finding unrelated to the implementation of the MF protocol. These findings may be a reflection of the differences in patients' demographics between the 2 periods, as patients in the post-MF period were noted to have significantly higher parity, thus increasing the indication for repeat caesarean section.

BG control remained comparable and satisfactory across both study periods. During the post-MF period, there were fewer women relying on lifestyle measures alone for management of their GDM

(not statistically significant). It is possible that women with more marginal degrees of hyperglycemia were started on pharmacotherapy once metformin was offered as an alternative treatment option to patients; however, the older age of the women in the post-MF period may also explain the higher rates of pharmacotherapy. Introduction of the protocol has reduced the percentage of patients started on insulin by half, a finding that has significant implications for clinic efficiency. Initiation of insulin is a resource- and time-intensive process, necessitating individualized teaching sessions with physicians and diabetes educators. Patients taking insulin also require ongoing monitoring, as doses must be adjusted regularly to optimize BG control. In contrast, metformin can be initiated with a standardized prescription and patients tolerating their maximum daily dose require less frequent follow up. Upon analysis of patient survey results, we did not observe any associated decreases in wait times or length of clinic visits. However, it is important to note that these data are patient reported and also do not account for variations in patient load on any given clinic day.

Patient survey responses revealed a statistically significant increase in patient satisfaction scores at the clinic after introduction of the MF protocol. It is difficult to comment on whether this increase in scores is clinically significant. In addition, there are many confounding factors that may have impacted these results, including staff turnover and adjustments in clinic scheduling and procedures over time. However, our results are consistent with previous findings showing patients to be more accepting of metformin therapy. In a randomized, controlled trial comparing metformin and insulin use for management of GDM in 751 women, 77% of patients on metformin said they would choose metformin therapy again, whereas 27% of patients receiving insulin said they would choose insulin again ($p<0.001$) (4). Patients receiving metformin were also more likely to choose “taking medication” the easiest part of their GDM treatment (59.0% vs 35.3%, $p<0.001$).

To our knowledge, this is the first study to evaluate a “real-world” clinical protocol that offers metformin as a first-line pharmaceutical therapy for management of GDM. The strengths of this study are that it consisted of an unselected, diverse cohort of patients with GDM and that it was carried out in a standard-care practice setting. This study is limited by its retrospective design, which resulted in some missing data upon chart review, and baseline differences between the 2 patient populations. Allocation to metformin was neither randomized nor blinded, allowing for potential biases in outcome results. The patient satisfaction survey utilized in this study was developed by clinic staff as part of a quality improvement initiative and is not a clinically validated tool. The study is also lacked a power analysis, which would help better assess the adequacy of the study sample size.

Conclusions

The results of this trial support the safety and efficacy of a metformin-based clinical approach for management of GDM, and also highlight its potential for improving patient satisfaction and factors of clinic efficiency through reduction in insulin starts. The outlined MF protocol may provide a framework for future adoption of metformin use into routine clinical practice for management of GDM.

Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Diabetes* at www.canadianjournalofdiabetes.com.

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Author Disclosures

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Author Contributions

All authors reviewed the final draft. All authors contributed to the design and implementation of the research, to the analysis of the results and to the writing of the manuscript.

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