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In This Issue

MESSAGE FROM THE EDITOR-IN-CHIEF

Welcome Clinical & Scientific Section Members

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With this issue, the editorial board welcomes the members of the Clinical & Scientific Section (C&SS) to *The Diabetes Communicator (DC)*. As we merge the Diabetes Educator Section and the C&SS into one professional membership, the Professional Section, changes will occur as the new membership is structured. This gives us the opportunity to make changes to DC to ensure our publication meets the needs of all healthcare professionals involved in working with and educating people with diabetes. We encourage all professional members to fill out our survey www.surveymonkey.com/r/PNCLWMF to help guide us in how DC will change.

EDITORIAL

Big Babies, Big Problem? Management of Diabetes in Pregnancy

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Melanie Snider

Ellen Kirk-Macri

In this issue of *The Diabetes Communicator* (DC), we will hear from experts in the field of diabetes and pregnancy. The 2013 Clinical Practice Guidelines (CPGs) reminds us of the importance of care of women living with diabetes before, during and after pregnancy.

We will hear from Drs. Mary Lu and Ruth McManus as they explore the history of why and how the CPGs concerning this topic were developed and discuss some of the controversy. Dr. Denice Feig shares an update on two exciting research trials currently underway in Canada. Read on to find out how the Metformin in Women with Type 2 Diabetes in Pregnancy (MiTY) trial and the Continuous Glucose Monitoring in Women with Type 1 Diabetes in Pregnancy Trial (CONCEPTT) may provide evidence toward improving the rates of adverse outcomes in women with pre-existing diabetes.

Kimberley Nix and Dr. Jillian Coolen share new and updated recommendations for preconceptual folic acid for women with pre-existing diabetes. What should we be telling our patients about folic acid and what are the benefits?

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FROM THE CHAIR'S DESK

The Summer Winds Are Changing

Michelle Corcoran, RD, CDE
Chair, Diabetes Educator Section

Change is inevitable and constant; we see it every day. Speaking of change, we have now evolved into one professional membership structure with our professional colleagues from the Clinical & Scientific Section. We are transforming into a bigger (and better!) entity for professional collaboration within the Canadian Diabetes Association (CDA) (see Rema Sanghera's article on page 6).

Hopefully, you have all taken the chance to visit the new Professional Section website at www.diabetes.ca and have had the opportunity to renew your professional membership online. A great new feature is that we can now renew at any time of the year. Remember to entice your friends and colleagues who aren't already members with the benefits of professional membership!

As we reflect on what we have done, we are now seeing what we can do; progress in research has given us more opportunities to improve the lives of people living with diabetes. This is evident in the fantastic articles in this issue that highlight pregnancy and diabetes as well as include several updates from other important clinical research. Definitely an informative read!

Be sure to touch base with your chapter chairs and executives about the goings-on at the Leadership Forum, which was held on June 4 to 5, 2016, in Toronto. Updates from liaisons, committees and your national executive were given, and the ever-so valuable learning and networking opportunities were welcome. Thank you to Shelley Jones, chair-elect, for organizing this fantastic weekend event. Well done!

At the national executive level, we had some recent executive member changes. Director of communications, Christina Vallaincourt, stepped down after taking on a new employment opportunity. We thank Christina for her dedication and contributions to *The Diabetes Communicator* and the national executive. We will miss you, but we won't say goodbye, only, until we meet again! In the interim, Amy Hui will take on the role of director of marketing and communications; thank you, Amy, for taking on this new portfolio as we move toward our new professional governance model.

Stay tuned for updates on the 2016 Diabetes Educator Day, November 2. Amy Hui, along with the marketing committee, are pulling together the poster and information. Start your planning now to promote diabetes educators in your area. Celebrate your successes!

> "Visit the new professional website at www.diabetes.ca and renew your professional membership online."

Lastly, I wanted to take a moment to reflect on volunteerism. As we move to new heights in our professional membership within the CDA, take the time to remember where we came from over 40 years ago.

Thank you to all of our volunteers. As volunteers, many of you tirelessly give your time and energy to create new resources, review journal research articles, attend expos and community events, and so on. But please remember to take time for yourselves, your family and other loved ones. I want to inspire you to be involved, and stay involved, with the CDA and our new professional membership. We need our volunteers to bring to life the wonderful wealth of resources we have created, but it is important to balance home life with work and volunteering. A sincere thank you for all that you do!

See you in Ottawa in October! If you have any questions, please feel free to contact us at professional.membership@diabetes.ca.

MiTy and CONCEPTT: Pregnancy Trials to Improve Outcomes!

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Building a Successful Professional Section Chapter Resource on Diabetes365

There was a delay in putting this resource online. The content of this manual was to appear on the Canadian Diabetes Association website in a web directory format. Due to the upcoming combined membership of the Diabetes Educator Section and the Clinical & Scientific Section, the professional website will be redesigned to meet the needs of membership renewal and resource sharing.

The Temporary Solution
During website reconstruction, the content from the "Building a Successful Professional Section Chapter" will be put on Diabetes365. Please find these files at: diabetes365.timedright.com/app/login.html.

Note that the access is only for active professional members.

Just as overall rates of diabetes are soaring, so too are rates of women with type 1 and type 2 diabetes in pregnancy. A recent population-based trial looking at incidence rates in all of Ontario found that the rates of pregnant women with pre-existing diabetes (type 1 and type 2) had doubled from seven per 1000 in 1996 to 15 per 1000 in 2010 (1). For women aged 30 years or older, the rate was as high as 19 per 1000, or almost two per cent! Women with type 1 or type 2 diabetes have high rates of adverse pregnancy outcomes with increased rates of gestational hypertension, preeclampsia, preterm delivery, congenital anomalies, macrosomia, neonatal hypoglycemia, respiratory distress syndrome and perinatal mortality. However, healthcare professionals are often more concerned about the pregnancies of women with type 1 diabetes than about those with type 2 diabetes. But is this justified? In a systematic review and meta-analysis of studies comparing characteristics and outcomes in women with type 1 versus type 2 diabetes in pregnancy, women with type 2 diabetes tended to be older (33.3 years of age versus 28.8 years), heavier (body mass index [BMI] of 30.2 versus 24.2), have had diabetes for a much shorter time (5.9 years versus 11.9 years), and were less likely to have microvascular complications at the onset of pregnancy (2). They also tended to have more chronic hypertension (11% versus 5.5%), they came less often for prepregnancy care (18.8% versus 34.8%) and despite having better glycemic control throughout pregnancy, they had an equal rate of congenital anomalies, and a higher rate of perinatal mortality compared to women with type 1 diabetes! This may be due to their reduced rate of pregnancy planning as well as the high rates of obesity and social disadvantage, all of which are associated with poor fetal outcomes (3).

How can we lessen the rate of adverse outcomes for women with pre-existing diabetes? Two randomized trials may help: Metformin in Women with Type 2 Diabetes in Pregnancy (MiTy) and the Continuous Glucose Monitoring in Women with Type 1 Diabetes in Pregnancy Trial (CONCEPTT), which are currently underway in Canada.

In the MiTy trial, women with type 2 diabetes in pregnancy are randomized to receive either metformin one gram twice a day or placebo, in addition to their usual insulin therapy. There are several theoretical reasons why adding metformin to insulin may be beneficial. Metformin is a biguanide that reduces hepatic gluconeogenesis and improves insulin resistance. This action will improve glycemic control and may result in lower maternal insulin doses. Women with type 2 diabetes are already quite insulin resistant outside of pregnancy, and become even more insulin resistant during pregnancy. Very high insulin doses are often needed to compensate for this insulin resistance in order to maintain good glycemic control. Very high insulin doses may lead to discomfort, poor absorption, poor compliance and increased cost. The addition of metformin to insulin for patients who are not pregnant has resulted in reductions in insulin requirements of up to 30 per cent (4). We hypothesize that the addition of metformin will reduce insulin doses in women with type 2 diabetes in pregnancy.

High insulin doses may also contribute to excess weight gain in already overweight and obese women. There is growing evidence that excess weight gain during pregnancy (above the recommended Institute of Medicine recommendations) is associated with adverse pregnancy outcome, especially in women with type 1 and type 2 diabetes (5,6). As well, gaining five kilograms or more above that which is recommended during pregnancy is more likely to lead to failure to lose the weight after delivery. This would have detrimental consequences for women with type 2 diabetes who are often already overweight or obese. A recent trial of metformin in obese women without diabetes found reduced maternal weight gain in the metformin group (7). The Metformin in Gestational Diabetes (MiG) trial, a study of metformin use in women with gestational diabetes, found similar results (8).

Adding metformin may also reduce rates of preeclampsia. There is some evidence that preeclampsia

is associated with insulin resistance that predates the preeclampsia, suggesting a possible etiological role. Therefore, reducing insulin resistance may lower rates of preeclampsia. A recent study looking at metformin in obese women found a reduction in preeclampsia in the metformin group, compared to those on placebo (7).

It is known that metformin readily crosses the placenta. Another theoretical reason for the use of metformin during pregnancy may be an improvement in insulin resistance in the fetus. Treatment with metformin may reduce insulin resistance and hyperinsulinemia in the offspring, and thus reduce macrosomia and other neonatal complications. There is also evidence that offspring of mothers with diabetes are at increased risk of obesity and diabetes themselves later in life, perhaps due to the hyperinsulinemia in utero (9). Treatment with metformin may decrease this "fetal programming" by reducing the insulin resistance and insulin levels in utero. MiTy Kids is a cohort study looking at the children of mothers in the MiTy trial to see if there is a difference in adiposity in the children of mothers exposed to metformin during pregnancy, compared to children of mothers who are not exposed.

MiTy has 21 centres across Canada and one centre in Australia, with four more to start shortly. MiTy has enrolled 360 women and aims to enrol a total of 500 women. At this time, there are no large, placebo-controlled trials to answer this question and MiTy will help guide the treatment.

Women with type 1 diabetes also have increased adverse pregnancy outcomes, and they struggle to achieve euglycemia while trying to minimize episodes of hypoglycemia when planning pregnancy and during pregnancy. Are they achieving euglycemia? In a study looking at glycemic profiles in women with type 1 and type 2 diabetes, women spent nine hours per day hyperglycemic (blood sugar level greater than 7.8 mmol/L), three hours per day extremely hyperglycemic (greater than 11.1 mmol/L), 3.5 hours per day hypoglycemic (3.0 mmol/L) and 1.1 hours per day with nocturnal hypoglycemia (10). Clearly we are not achieving euglycemia. What can help?

A continuous glucose monitor (CGM) measures interstitial glucose continuously and displays a reading every five minutes. In a study of blinded CGM where women with diabetes wore the CGM one week per month and then downloaded results and reviewed them with their physician, women wearing the CGM had infants with less macrosomia, compared to women under the usual care (11).

Real-time (RT) CGM allows women to see their glucose values and trends in real time and take immediate action to correct blood glucose levels trending up or down. A study of intermittent RT-CGM in women with diabetes during pregnancy failed to show a difference in glycemic control or in fetal outcomes (12).

The CONCEPTT trial is attempting to see whether women with type 1 diabetes who are planning a pregnancy, or who are early in their pregnancy, would benefit from the use of an RT-CGM worn continuously. It is a multi-centre, multinational, randomized trial with centres in Canada, the United Kingdom, Spain, Italy and the United States, where 110 women with type 1 diabetes who were planning pregnancy, and 215 women who were in early pregnancy, were randomized to receive either RT-CGM or their usual care. The primary outcome is a change in glycated hemoglobin. Secondary outcomes will include the effects of CGM on maternal and fetal outcomes and differences between women using a pump and a CGM versus multiple daily injections and CGM. The CONCEPTT trial completed its recruitment and will complete the analysis by 2017. We look forward to sharing these results with you!

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The Canadian Diabetes Association Professional Section Membership Is Coming in June 2016!

Rema Sanghera, MA, RD, CDE
Director of Membership, Diabetes Educator Section; on behalf of the CDA Professional Section Membership Task Force

For over 40 years, the Diabetes Educator Section (DES) and the Clinical & Scientific Section (C&SS) have existed side by side. In April 2015, at the Canadian Diabetes Association (CDA) national annual general meeting, the decision was made to combine the two sections. A driving force behind the decision is the belief that we can be stronger together, while maintaining the special interest of each section. An eight-member task force with representatives from the DES, C&SS and CDA was formed. To date, the task force has developed the new membership structure, while the work on governance continues.

Combined membership was introduced at the Leadership Forum in September 2015, and has been discussed regularly in *The Diabetes Communicator*. However, a question that routinely comes up is: why the move to one professional membership?

"It makes sense. In our job, we work in interdisciplinary teams with the goal of helping people with diabetes live well. Our conference, guidelines and resources are collaborative. We are all part of CDA. So why work in silos? Our future is joint membership." – Michelle Corcoran, DES chair

"One vision, one voice." – Lori Berard, past DES chair

"The main benefit of combined membership is to facilitate multidisciplinary approach to clinical care, advocacy and research." – Jay Silverberg, C&SS past chair

"Given the multidisciplinary nature of diabetes research and care, combined membership will hopefully increase engagement with primary care. Current/future special interest groups will provide opportunities for multidisciplinary collaboration, which was not easy with our previous structures. This is an exciting opportunity, which may help expand the scope and influence of the professional section to improve the lives of people with diabetes." – Peter Senior, C&SS scientific vice chair

"The joint membership aligns with CDA's vision to have diabetes care delivered by interprofessional teams. This will allow healthcare providers who help people living with and at risk of diabetes to network seamlessly. The greatest benefit will be to the patients who are receiving care from team members." – Jovita Sundramoorthy, vice-president of research and education, CDA

Is the change in professional membership "change for the sake of change or change for a reason"? You decide.

We welcome all thoughts and comments. Please email us at professional.membership@diabetes.ca.

Gestational Diabetes: A Narrative Account Linking Past to Present

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Gestational diabetes mellitus (GDM) is commonly defined as glucose intolerance discovered during pregnancy. The evolution of GDM diagnostic criteria and treatment has been remarkable over the past five decades, and is particularly notable for controversy and strong opinions. The following summary provides a review of important highlights along the GDM journey to 2016.

What Came Before O'Sullivan and Mahan?

John (Sean) O'Sullivan and Clare Mahan began reporting on GDM during the early 1960s. They are rightly remembered as pioneers in the field, and more will be said about their work later. However, there is a backstory of important milestones that should be noted.

Early in the 20th century, Dr. Priscilla White published seminal work in the field of diabetes and pregnancy, working out of the Joslin Diabetes Center in Boston, Massachusetts, USA. At that time, pregnancy complicated by diabetes mellitus (DM) was dangerous, and frequently fatal, for infant and mother. Women with DM were advised not to conceive; physicians were known to advocate for therapeutic abortion when conception occurred. In 1928, Dr. White first documented frequencies of adverse perinatal outcomes (miscarriage rates of 16 per cent and stillbirth rates of 25 per cent) for pregnant women with overt DM. She developed a classification system that was the basis for the future study of GDM in which she discerned that women only with DM during pregnancy (White class A) should be considered separately from women with pre-existing DM (classes B-F) (1).

As the century progressed, further evidence emerged linking high maternal blood glucose (BG) levels to poor pregnancy outcomes. Three reports were offered for illustration; it was observed that some women diagnosed with DM later in life had a history of delivering a macrosomic infant (2); Hoet and Lukens (3) observed that higher BG levels in pregnancy were detrimental to infant outcomes, but did not definitively separate DM from GDM. Later in the decade, pregnant women with abnormal (but not DM-range) BG levels were identified and treated with insulin (4).

O'Sullivan and Mahan

O'Sullivan and Mahan worked in Boston during the mid-20th century. O'Sullivan was a diabetes clinician and researcher, and Mahan was a statistician. The paper that was most influential—and that subsequently became a source of controversy—was published in 1964 (5).

In the 1964 study, 752 pregnant women without DM underwent a 50-gram glucose load followed by a 100-gram oral glucose tolerance test (OGTT). Venous blood samples were taken fasting, one, two and three hours post-glucose load. Most women were tested in the second or third trimester. Glucose results were plotted as a normal curve; results were categorized as being one, two or three standard deviations above the mean. Next, these study results were applied to a second set of OGTT results for 1013 women who were followed for up to eight years to document the timing of postpartum DM onset. Thereafter, maternal postpartum DM risk was correlated with pregnancy OGTT results. The authors concluded that the presence of two BG results, that were at least two standard deviations above the mean for an OGTT during pregnancy, would best predict post-partum onset of DM.

Why was this publication so influential for the next 40 years? Answers may lie in the following:

- That investigation was the first to apply a firm statistical foundation to OGTT results based on a hard outcome—in this case, the risk for developing future DM.
- Use of the 100-gram OGTT in two large cohorts like that gave test results primacy over competing glucose testing (at the time, multiple methods of glucose tolerance evaluation were in play, including tolbutamide or cortisol modified tests [6,7] and intravenous-administrated glucose tests [8]).

- Furthermore, O'Sullivan et al went on to apply their GDM criteria to investigate insulin use in lowering the risk for infant macrosomia (9).

Later 20th Century

The latter years of the 20th century witnessed a cacophony of competing GDM criteria. In 1991, O'Sullivan summarized studies reporting the risk for DM after GDM, wherein he found that researchers had used at least 11 differing GDM diagnostic criteria (10). For example, outside of North America, World Health Organization (WHO) criteria were often used, where the diagnosis of GDM was based upon non-pregnancy 75-gram OGTT criteria; in North America, there were two major competing sets of 100-gram OGTT criteria known as National Diabetes Data Group (NDDG) and Carpenter and Coustan (11-12).

Five international workshops (1997 to 2005) were convened to search for some consensus around GDM diagnosis and treatment. Consensus about diagnostic criteria was partial at best—in the most recent of these workshops (2005), criteria for both the 75-gram and 100-gram oral glucose load were offered as options, with or without a preceding 50-gram screen test (13).

More Controversy

By the mid-1980s, the medical community began having second thoughts about somewhat overlooked difficulties with GDM diagnostic criteria (14). The major concerns included the following:

- The O'Sullivan criteria for GDM had been based on predicting subsequent post-partum maternal risk for "true" diabetes, but the criteria were predominantly used to predict neonatal outcomes.
- The 1965 O'Sullivan venous glucoses were analyzed by a different method than present-day plasma glucoses. A mathematical correction factor had been used to translate their venous numbers into plasma numbers, without any proof that this conversion was valid.
- Hyperglycemia that fit GDM diagnostic criteria wasn't the only cause of large-for-gestational-age babies, so it was suspected that glucose would be a continuous variable associated with large offspring, without definitive thresholds (15).

Therefore, particular discomforts about the diagnosis of GDM could be summarized in two major areas: hard diagnostic criteria based on fetal outcomes were needed, as was definitive proof that treatment of elevated BG levels in GDM pregnancies made a difference to outcomes.

Stepping into the 21st Century: Helpful Outcome Studies

In 2005, Langer et al (16) published an observational study of treated versus matched, untreated GDM women. Untreated GDM was found to be associated with a two- to threefold increase in perinatal morbidity. Notably, children born to untreated mothers with even mild glucose intolerance experienced more adverse outcomes.

Also, in 2005, the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) reported a randomized trial of treatment versus routine care in GDM for 1000 women (17). Not only were serious perinatal complications lower in women with treated GDM versus controls (one per cent versus four per cent), but women in the GDM treatment cohort reported improved health-related quality-of-life scores.

In 2009, the Maternal Fetal Medicine Units Network (MFMU) completed a randomized trial of 958 women, investigating whether treatment of mild gestational diabetes conferred any benefit for perinatal outcomes (18). Mild GDM was defined as abnormal glucose tolerance test results, but with fasting BG at less than 5.3 mmol/L. Treatment was associated with a significant decrease in rates of caesarean birth, macrosomia, shoulder dystocia and maternal hypertensive disorders.

These three seminal studies confirmed that treatment of GDM—even if "mild"—is beneficial for mother and offspring. Frustratingly, however, all studies used differing criteria for GDM diagnosis, which brings us to the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study.

HAPO: Hopes and Hesitations

In 2008, the HAPO study cooperative reported pregnancy outcomes in 23,316 women (19). HAPO was an observational, multicentre and multiethnic trial using a 75-gram, two-hour OGTT to find out what glucose levels would predict adverse fetal outcomes. Clinicians were blinded to the OGTT results, and women with fasting BG of 5.8 mmol/L or higher, or a two-hour BG of 11.1 mmol/L or higher were excluded. Results

were both encouraging and frustrating: there was no definite BG threshold level (for any of fasting, one- or two-hour glucose values) at which adverse perinatal outcomes became evident.

What did all this mean, and where would it lead? The International Association of the Diabetes and Pregnancy Study Groups (IADPSG) founding members moderated the international discussion generated by the HAPO results, aiming to achieve consensus around BG thresholds (20,21). The GDM diagnostic criteria that are now known as the IADPSG (or HAPO) criteria are based on the OGTT glucose levels associated with an odds ratio of 1.75 times the mean for macrosomic offspring, or elevated neonatal insulin (reflected by cord c-peptide) levels.

Although there is obvious appeal to having one set of worldwide GDM criteria, based on a simple one-step fasting 75-gram OGTT, unresolved concerns remain:

- HAPO was an observational study that did not compare outcomes according to different treatment strategies (specifically, the new and old OGTT criteria).
- Using IADPSG criteria results in a doubling of GDM prevalence (labelling approximately 18 per cent of pregnancies as GDM), which has major financial implications for both developed and developing countries (22,23).
- Furthermore, studies using IADPSG criteria reported conflicting results: both better (24) and worse pregnancy outcomes (25). It appears likely that only results from large, randomized treatment outcome studies using the IADPSG OGTT criteria will settle the ongoing controversy over diagnostic criteria.

Other Valuable Results Appearing in Recent Decades

The following are perhaps less controversial, but also important findings during the GDM journey:

- Adjusting insulin to achieve post-prandial rather than pre-prandial blood glucose control results in better fetal outcome (26).
- The Metformin in Gestational Diabetes (MiG) trial concluded that metformin is a safe option for treating GDM, although 46 per cent of women randomized to metformin ended up needing insulin as well (27).
- Glyburide during pregnancy has been an appealing option, although the final word on its safety remains unknown (28).

Reflecting on the Future

Despite the controversies noted above, the present situation is much clearer for pregnant women and their medical caregivers, because GDM treatment options and infant outcomes are vastly better than the early 20th century. Much more is known about the need to treat GDM, but also about how to investigate and seek consensus on study findings. Perhaps the following three items represent a clinical wish list for the next important steps along the GDM journey:

- A large-scale randomized study comparing IADPSG to existing diagnostic criteria with regard to infant outcomes.
- Definitive documentation of the effects of GDM treatment on the long-term metabolic health off offspring.
- Widespread implementation of DM risk-reduction strategies for women after GDM.

Ironically, although O'Sullivan and colleagues were originally interested in GDM as a marker for developing future DM, 60 years after their publications, we lack proven programs to help this population of women avoid developing type 2 diabetes.

There has been much progress in our understanding of GDM in the past few decades. The practitioners who counsel women with GDM look forward to future studies that will further ground the daily clinical decisions on evidence-based, practice-changing research outcomes.

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EDITORIAL...CONTINUED FROM PAGE 1

Amanda Bawdon's article highlights some key educational points regarding the benefits of breastfeeding for women and their children.

As educators we learn from our personal as well as patient experiences. What happens when the diabetes educator is the patient? Jodi Thorimbert generously shares her experience wearing an insulin pump during her pregnancy.

And then we look beyond our Canadian borders as Anne Belton shares an intriguing article on developing a model of care for gestational diabetes in India. This insight can assist us to reflect upon our role in Canada, especially when considering the needs of our growingly diverse populations.

Dr. Ronald Goldenberg provides us with an update on the pharmacological management of type 2 diabetes. Lastly, Jenna Anderson, Janelle Trifa and Robyn Patrick share a general overview from the pharmacy perspective for this topic. We all know this is an ever-changing area of diabetes education; therefore, this article is a must read!

The Autumn issue of DC will focus on the complications of diabetes. Do not be shy to contribute: www.diabetes.ca/communicator. Make this your DC!

Preconceptual Folic Acid Recommendations for Women with Pre-Existing Diabetes: Clarification of Conflicting Canadian Guidelines

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Preconceptual folic acid supplementation is widely known to assist in the prevention of neural tube defects (NTDs) (1–6) and may be implicated in other congenital abnormalities (1,7). Pregnant women with pre-existing diabetes are considered to be at increased risk for congenital anomalies, such as neural tube defects (NTDs) (8).

For women with pre-existing diabetes, the 2013 Canadian Diabetes Association guidelines recommend supplementation of diet with a multivitamin containing five milligrams of folic acid at least three months preconception and continuing until at least 12 weeks post-conception (8). In contrast, the 2015 Society of Obstetricians and Gynaecologists of Canada (SOGC) clinical practice guidelines recommend one milligram (1). The dissonance between the two guidelines has led to some clinical confusion, which we hope to clarify.

How Does Folic Acid Prevent NTDs?

NTDs affect 5.8 of 10,000 children in Canada, with the Atlantic provinces having the highest prevalence (9). NTDs arise due to failure of the neural tube to close between day 25 to day 27 of gestation (10), with anencephaly and spina bifida as common presentations (11).

Evidence of the effectiveness of increasing serum folic acid to prevent NTDs has existed since the 1970s (12). Folic acid directly affects the neurulation-stage embryo, producing pyrimidines and purines for DNA replication during cell proliferation and donating methyl groups to macromolecules including DNA, proteins and lipids (13).

Why Are Women with Pre-Existing Diabetes at Increased Risk for NTDs?

Diabetes mellitus is considered a risk factor for NTDs (9), with an increased risk of one per cent when the mother has poor glycemic control (14). Animal studies would suggest that this increased risk is not due to folate deficiency, but rather induction of oxidative stress, which activates cellular stress signalling leading to dysregulation of gene expression (15) and excess apoptosis in the target organs, including the neural tube and embryonic heart, and/or hyperglycemia leading to faster embryonic development during the process of neural tube closure and delayed midbrain fold elevation (16). Importantly, a 2016 animal study demonstrated that folic acid provided minimal effect on preventing hyperglycemia-induced NTDs in chicken embryos, indicating that excessive folic acid supplementation may not prevent the additional risk of NTDs in pre-existing diabetes (17).

How Can Women with Pre-Existing Diabetes Reduce Their Risk for NTDs?

Maternal preconceptual supplementation with folic acid has been shown to lower the occurrence and recurrence of NTDs (3). The majority (99.7 per cent) of women in North America have normal serum folate levels (18), and most women who have a child with NTD had normal red blood cell (RBC) folate levels during pregnancy (13). While limited, there is evidence that blood folate levels may not differ between women with and without diabetes (19). It appears that hyperglycemia, rather than folic acid is the major risk factor that leads to the increased risk for NTDs in women with pre-existing diabetes (14). Therefore, the most important strategy for the prevention of congenital anomalies, including NTDs, for women with pre-existing diabetes should be excellent glycemic control, ideally with a glycated hemoglobin of less than seven per cent preconception.

The SOGC changed the risk stratification for women with pre-existing diabetes from high risk requiring five milligrams of folic acid preconception

in 2003 to moderate risk requiring one milligram of folic acid in 2015. In addition, they described the use of RBC folate levels to guide folic acid supplementation, with one milligram recommended for an RBC folate level less than 906 and 0.4 mg for levels greater than 906 (1).

Is There Risk with High-Dose Folic Acid Supplementation?

While low-dose folic acid supplementation is considered safe, the safety of high-dose folic acid is still being established, with some evidence of potential harm (2,6). Specifically, there is some recent evidence that high levels of folic acid throughout gestation may have adverse effects on fetal brain development (20). Drug interactions for women on multiple medications may also be problematic, and must be considered on an individual basis (20). While the risk is likely low, best practice may be to prevent the overprescription of folic acid.

Conclusion

Women with pre-existing diabetes are considered to be at a moderately increased risk for NTDs. As recommended by the SOGC in 2015, in addition to a diet of folate-rich foods, they require daily oral supplementation with a multivitamin containing 1.0 mg of folic acid, beginning at least three months before conception until 12 weeks' gestational age for NTD prevention (8). If folic acid deficiency is suspected, a serum RBC folate level can be performed to determine if additional folic acid supplementation is required. As hyperglycemia is the major teratogen in the pregnancies of women with pre-existing diabetes, the most important preventive strategy is euglycemia before and during pregnancy.

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Integrating the "Pharmacologic Management of Type 2 Diabetes: 2016 Interim Update" into Practice

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Case Presentation

A 63-year-old South Asian male has had type 2 diabetes for six years, and is treated with 1000 milligrams of metformin twice a day. He has a history of prior myocardial infarction and underwent coronary artery bypass surgery two years ago. His glycated hemoglobin (A1C) is 8.1 per cent, fasting plasma glucose 8.8 mmol/L and estimated glomerular filtration rate (eGFR) 74 mL/min. What antihyperglycemic agent should be added to metformin?

Introduction

Whenever updated data has the potential to drive a change in clinical practice, the *Canadian Diabetes Association* 2013 *Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada* includes a provision to update individual chapters with an interim update prior to the publication of the next complete version of the guidelines.

The EMPA-REG OUTCOME trial, the first completed cardiovascular (CV) outcome study utilizing a sodium-glucose co-transporter 2 (SGLT2) inhibitor, demonstrated CV superiority, justifying an update to the chapter on the Pharmacologic Management of Type 2 Diabetes. Other completed CV outcome trials have demonstrated the CV neutrality of three dipeptidyl peptidase-4 (DPP-4) inhibitors (alogliptin, saxagliptin, sitagliptin) and one glucagon-like peptide-1 (GLP-1) receptor agonist (lixisenatide), data worth considering when choosing antihyperglycemic agents in the management of type 2 diabetes. The 2016 interim update integrates the data from these trials into the pharmacologic algorithm and the table of antihyperglycemic agents.

EMPA-REG OUTCOME

The EMPA-REG OUTCOME trial included over 7000 patients with type 2 diabetes and established cardiovascular disease (CVD), such as prior myocardial infarction (MI), coronary artery disease, unstable angina, stroke or occlusive peripheral arterial disease. They were randomized to two different doses of empagliflozin (10 milligrams or 25 milligrams) or placebo on top of standard care, and the median observation time was 3.1 years. Only two per cent of individuals were drug naive and over 80 per cent had diabetes for more than five years. A1C was between seven per cent and 10 per cent at study entry, and the mean baseline A1C was 8.1 per cent.

The primary composite CV outcome (CV death, nonfatal MI or nonfatal stroke) was lower in the pooled empagliflozin group compared to the placebo group (10.5 per cent versus 12.1 per cent, hazard ratio 0.86, P=0.04), proving the superiority of empagliflozin in this patient population. Empagliflozin therapy was also associated with significant relative risk reductions of 38 per cent for CV death, 35 per cent for hospitalization from heart failure and 32 per cent for total mortality. There was no reduction in nonfatal MI or nonfatal stroke. There were some metabolic benefits with empagliflozin versus placebo on top of standard care, including an A1C reduction of –0.4 per cent, systolic blood pressure reduction of –4 mmHg, and a 2.5 kilogram weight loss. These changes cannot account for the major CV benefits shown in the EMPA-REG OUTCOME trial. The CV benefit of empagliflozin was not due to a reduction in atherosclerosis-related cardiovascular events. Osmotic diuresis as well as other unknown mechanisms may have contributed to the benefit of empagliflozin on heart failure and related outcomes. While genital infections occurred at a higher rate in the empagliflozin-treated patients, there were no increases with other adverse events.

Interim Update Highlights

Prior to the EMPA-REG OUTCOME trial, there was little evidence that other antihyperglycemic agents provide a cardiovascular benefit in patients with established CVD. Furthermore, when individualizing antihyperglycemic agent therapy for type 2 diabetes, the potential benefit on cardiovascular outcomes should be considered a priority, since 40 to 60 per cent of these patients will die of CVD.

Recognition of Outstanding 2016 National Canadian Diabetes Association Award Recipients!

Congratulations to all the 2016 Canadian Diabetes Association national award recipients and, in particular, our very own professional section members highlighted below.

These awards were presented at the regional volunteer appreciation events during National Volunteer Week, April 10 to 16, 2016. Well-deserved recognition to all!

Charles H. Best Award
Dr. Alice Cheng

Frederick G. Banting Award
Dr. Jonathan McGavock

National Volunteers of the Year
Kathryn Arcudi, Louise LeFebvre and Karen McDermaid

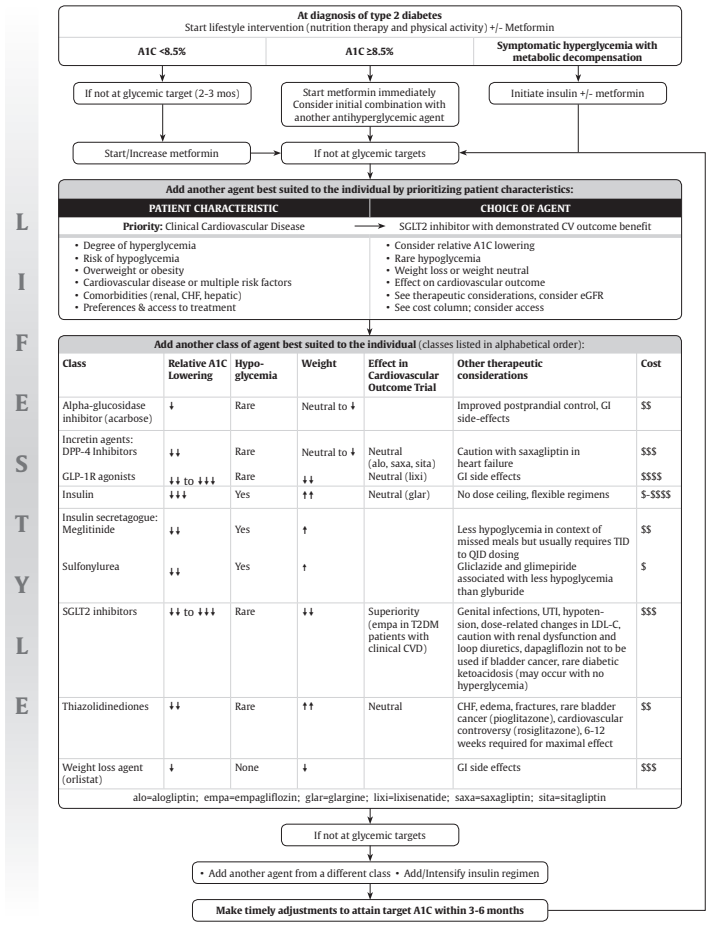

Figure 1. Management of hyperglycemia in type 2 diabetes. A1C, glycated hemoglobin; CHF, congestive heart failure; CVD, cardiovascular disease; DPP, dipeptidyl peptidase; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; GLP-1R, glucagon-like protein-1 receptor; LDL-C, low-density lipoprotein cholesterol; SGLT2, sodium glucose link transporter 2; T2DM, type 2 diabetes mellitus; UTI, urinary tract infection.

Therefore, the results of the EMPA-REG OUTCOME trial have been integrated into the pharmacotherapy algorithm by prioritizing the use of an SGLT2 inhibitor with proven CV outcome benefits in patients with type 2 diabetes and clinical CVD who are above their glycemic target with current antihyperglycemic agents. CV outcome trials with other SGLT2 inhibitors are ongoing, with results expected between 2017 and 2019, so at this juncture, it is unknown if the other members of this class (canagliflozin, dapagliflozin) provide the same CV benefit as empagliflozin.

The algorithm for the management of hyperglycemia in type 2 diabetes is summarized in Figure 1. A new addition for individualizing the treatment choice is prioritization of clinical CVD as a patient characteristic with recommendation of an SGLT2 inhibitor based on the EMPA-REG OUTCOME trial. Since several CV outcome trials with various antihyperglycemic agents have been completed with type 2 diabetes patients who have either CVD or multiple risk factors, the presence of CVD or multiple risk factors was added as a patient characteristic when considering the potential effect of antihyperglycemic agents on CV outcomes in such patients. A new column titled "Effect in Cardiovascular Outcome Trial" was added to the pharmacotherapy table in the algorithm to reflect data from randomized controlled CV outcome trials of antihyperglycemic agents (see Figure 1). This new column integrates data from such trials, and includes the CV neutrality of DPP-4 inhibitors (alogliptin, saxagliptin, sitagliptin), GLP-1R agonists (lixisenatide), insulin (glargine) and thiazolidinediones (pioglitazone, rosiglitazone), in addition to the CV superiority of SGLT2 inhibitors (empagliflozin).

Back to the Case Presentation

The patient meets the entry criteria from the EMPA-REG OUTCOME trial, with a history of type 2 diabetes, clinical CVD (prior MI and coronary artery

bypass grafting), exceeds glycemic targets, and has no contraindication to an SGLT2 inhibitor. Utilizing the new algorithm for the management of hyperglycemia in type 2 diabetes, the patient's clinical CVD is a priority, and he should be treated with an SGLT2 inhibitor with demonstrated CV outcome benefit. A starting dose of empagliflozin 10 milligrams should be initiated, per the CDA 2016 Interim Update.

To access the published interim update, please visit guidelines.diabetes.ca/browse/chapter13_2016. To use the updated interactive tool for the pharmacotherapy of type 2 diabetes, visit guidelines.diabetes.ca/bloodglucoselowering/pharmacologyt2. Additional practice tools and information, including the interim update can be found here: http://guidelines.diabetes.ca/2016update.

What Research Says About the Benefits of Breastfeeding and the Risk of Type 2 Diabetes

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Frequency of Gestational Diabetes and Risk Factors for Diabetes

Three to 20 per cent of pregnant women will develop gestational diabetes mellitus (GDM) or type 2 diabetes during pregnancy (1). These women have seven times the risk of developing type 2 diabetes in the next 10 years compared to women without GDM (2,3). The children of mothers with GDM also have a higher risk for obesity, impaired glucose tolerance and type 2 diabetes (4). The exciting news is that we, as educators, have an important role in assisting women with GDM to delay or prevent type 2 diabetes as a consequence of pregnancy (3) as well as to prevent obesity and chronic diseases in infants of GDM mothers (5).

The Benefits of Breastfeeding for the Baby

Breastfeeding lowers a baby's risk of obesity or developing chronic diseases in childhood and adolescence. Breastfed infants tend to grow more slowly and remain leaner in the first two years of life, compared to non-breastfed infants. Some attribute this to breast milk, which affects infant growth and regulates energy balance (5). Breastfeeding can reduce the risk of offspring being overweight later in life by 22 per cent to 24 per cent (5).

Breastfeeding is also associated with enhanced cognitive development, and helps protect against gastrointestinal infections, acute otitis media, respiratory tract infection and sudden infant death syndrome (6).

Known Benefits of Breastfeeding for Mom

Evidence shows that lactating women typically lose weight at the rate of 0.5 to 1 kilogram per month in the first four to six months (2), which is a quicker return to pre-pregnancy weight compared to mothers who do not breastfeed (5). Lifestyle interventions, such as healthy eating and exercise, can further promote weight loss (2). This might be due to increased insulin sensitivity and improved metabolism of glucose and lipids while breastfeeding (7,8). Childbearing women who breastfeed (not necessarily just GDM women) enjoy a 14 per cent reduced likelihood of type 2 diabetes per year, compared to non-breastfeeding mothers. Even an average of three months of breastfeeding per child is beneficial (8). Other benefits of breastfeeding include protection against the onset of breast and ovarian cancer, as well as decreased cardiovascular risk factors (5).

There is currently insufficient evidence to suggest that breastfeeding will decrease the onset of type 1 diabetes in mother or child; however, the research does emphasize how important it is for mothers with type 1 diabetes to breastfeed, despite the possible challenges (9).

Canadian Diabetes Association Clinical Practice Guidelines and Health Canada Recommendations

The Canadian Diabetes Association Clinical Practice Guidelines (CPGs) encourages women to breastfeed for at least three months to help "reduce neonatal hypoglycemia and offspring obesity, and

The Canadian Guide to Living Well with Diabetes

The Canadian Diabetes Association has developed a new resource for people living with diabetes. It shares valuable tips and tools that describe how diabetes affects the body, the potential complications associated with it and provides strategies for effective diabetes management.

Featured in the book:

- Information based on the Canadian Diabetes Association's Clinical Practice Guidelines for healthcare providers
- Colorful illustrations that highlight the key messages in each chapter
- A glossary of diabetes-related terms
- Easy-to-use tracking sheets for people with diabetes and their healthcare teams
- Helpful tips for day-to-day healthy living with diabetes, including nutrition, weight management and goal setting
- Educational summaries of the signs and symptoms of common complications associated with diabetes (neuropathy, retinopathy, and chronic kidney disease)

To order a copy of this valuable resource, please visit orders.diabetes.ca.

prevent the development of metabolic syndrome and type 2 diabetes in the mother" (10).

Health Canada and the World Health Organization recommend exclusive breastfeeding for the first six months, to be sustained for up to two years or longer with appropriate complementary feeding, and both organizations recognize very few situations where a mother cannot, or should not, breastfeed (6).

Breastfeeding Challenges in Women with GDM

The CPGs also acknowledges the difficulties related to mothers with GDM, attributing these challenges to "increased operative deliveries and obesity" (10). Increased challenges occur for women who experience infection of the nipples or poor infant sucking reflex; education about these to support mothers is needed (11). Finally, mothers with higher education levels, full-term vaginal delivery and early initiation of breastfeeding (before discharge at the hospital) are all predictive factors for breastfeeding two to six months postpartum (9).

So what does this mean in practice? During appointments with clients with gestational diabetes, I first go over the potential impact of GDM (specifically blood sugar levels) on both the mother and the baby. I ask if they plan to use formula or breastfeed, then ask if it is okay if I ask why they have chosen that method and if they would be open to hearing the benefits to breastfeeding. I quickly provide the benefits from the above research, but still ensure they will be supported in whichever method they choose. Again, asking the client's permission, I supply a list of local supports that include the public health nurse, breastfeeding consultants/supports and other local parenting resources to let them know there is someone they can call at any time to answer any questions they may have. Although the research is exciting, support is always more welcomed by clients than pressuring them.

In conclusion, along with education on self-management of blood glucose and lifestyle intervention being provided to women experiencing GDM, it is important to ask GDM clients who are pregnant if they are considering breastfeeding, and to provide the current research, while respecting their decision (12). GDM increases the risk of being overweight and developing impaired glucose tolerance, metabolic syndrome and type 2 diabetes after pregnancy, compared to the general population. It is essential to explain the immediate impact and lasting effect of breastfeeding on the future of these high-risk individuals (5). Breastfeeding is a low-cost intervention for women with high risk for developing type 2 diabetes (13). Prevention may be possible as the beneficial effects of breastfeeding may contribute to breaking the cycle of excess weight and diabetes that can occur among offspring of mothers with diabetes (14).

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Developing a Model of Care for Gestational Diabetes in India

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The prevalence of gestational diabetes mellitus (GDM) is increasing worldwide, with recent estimates set at about 16 per cent (1). In India, the prevalence has been reported as high as 35 per cent to 41 per cent in the north, and as low as 13 per cent in the south (2-4). Differences are likely due to different criteria used to diagnose GDM, as well as different socioeconomic settings in the different regions. Regardless of the prevalence, GDM remains a common condition and one that needs to be diagnosed and treated.

The International Diabetes Federation (IDF) developed a model of care (MOC) for low-resourced settings in India. The project "Women in India with GDM Strategy (WINGS)" began in 2010 and was completed at the end of 2015 in partnership with the Madras Diabetes Research Foundation in Chennai and with financial support from the Abbott Fund.

The project had four phases:

1. Situational analysis: the objective was to establish a baseline overview of screening and management protocols in India. This was accomplished through a literature review, a retrospective review of clinical records, a knowledge and attitude survey of pregnant women, a survey of healthcare professionals and a pilot screening study to determine which diagnostic criteria would be feasible and the best to use.
2. Development of the MOC: this model was set up to be evidence based, feasible and effective in resource-constrained settings. A curriculum was developed for training, and multidisciplinary teams were invited to Chennai for two-day sessions.
3. Implementation of the MOC: this required education of healthcare professionals and community health workers, and an evaluation of the effectiveness of the model in practise.
4. Dissemination of the MOC: the model was disseminated across India and to other low-resourced areas of the world.

Tools developed for the program include:

- A training manual for healthcare practitioners (a series of slides with teaching notes)
- The MOC implementation protocol (including algorithms for diagnosis, treatment and follow up)
- A training manual for community health workers
- A booklet for pregnant women (including activities for completion as the pregnancy progressed)
- A Snakes and Ladders game (for use in rural settings where groups of women gather)

The MOC was tested in seven health centres between November 2013 and December 2015. All women who attended at less than 28 weeks gestation were included in the study. Consent was obtained, and case report forms and food and activity questionnaires were completed, and pedometers were distributed. The International Association of the Diabetes and Pregnancy Study Groups (IADPSG) criteria were used for diagnosis. The pilot compared different diagnostic methods (non-fasting, using capillary blood, etc.) but none proved to be as accurate as the standard IADPSG criteria using venous blood (5,6). Of the 1200 women approached, 1124 agreed to be screened for GDM; 247 were diagnosed, and 212 were followed throughout their pregnancies under the MOC. Of those 212 women, 203 completed the post-natal follow up within the first year.

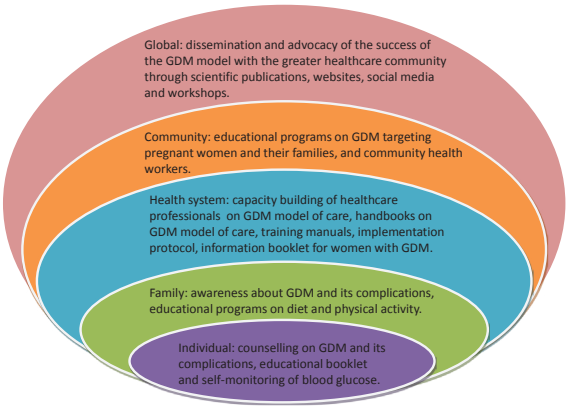

Figure 1: Framework of the "Women in India with GDM Strategy (WINGS)" project. Adapted with permission from the International Diabetes Federation. GDM Gestational diabetes mellitus.

Management

All women were counselled on meal planning and exercise. Questionnaires that had been previously validated in India were used to gather information at baseline and then repeated at 35 weeks to maximize the number obtained. We might otherwise have missed those who had delivered early or who had returned to their mothers for delivery (a common practice in India). The nutrition results showed some improvement, the use of refined cereals dropped somewhat, and the consumption of whole grains, milk products and dietary fibre increased significantly (7).

The physical activity questionnaire showed that women with GDM were significantly less active than those without GDM at baseline. Women were advised to be active 150 minutes a week, spread out over at least three days. The pedometers were an incentive to increase their activity. Because there are no known guidelines regarding how many steps are recommended during pregnancy, women were simply told to use the pedometer for three days, record the results (an average of the three days) and then try to increase the total by about 50 steps a day. Interestingly, 91 of 189 women used the pedometer and recorded the results. The number of steps taken did increase significantly (from 2262 to 2494), but still remained low (7).

Most women in this setting did not have blood glucose monitoring devices. The MOC, therefore, suggested that blood glucose testing (fasting and postprandial) be done every two weeks at the clinic. If the results were within target, this continued; if they were above target, insulin injections began, and monitoring increased to once a week until target levels were achieved, then reverted to every two weeks. About 15 per cent of the women started insulin during pregnancy. Metformin was not used in this study, although it is commonly used in low-resourced areas where insulin may not be available or where there is no education on the use of insulin.

The women received a booklet, which provided a review of the counselling they received. This booklet contained sections where they could keep track of meals, activities and blood glucose results. They were asked to bring the booklet to all appointments, so the physician could fill in the growth charts for the baby.

Results

The results of the study are being published later this year. However, we can share that the women in the study delivered babies as healthy as women without GDM and there was less macrosomia in the study population. Women with GDM did not deliver their babies earlier than women without GDM.

Post-Partum

The MOC requires a follow up at six to eight weeks, with an oral glucose tolerance test (OGTT) and a glycated hemoglobin (A1C) test. Almost 80 per cent of the women had the tests done before 12 weeks post-partum, another 15 per cent came back within one year. This was achieved through frequent reminders from the study staff and, in a few cases, home visits were done to collect samples. Our results showed dysglycemia in 12.3 per cent of the women who returned back before 12 weeks and in 7.9 per cent of women who came later. In total, at one-year postpartum, 20.2 per cent of women had some form of dysglycemia (impaired fasting glucose [IFG], impaired glucose tolerance [IGT], both IFG and IGT, type 2 diabetes). Only body mass index at the initial visit greater than 25 kg/m^2, A1C at the initial visit and birth weight greater than 3.5 kilogram were significantly associated with postpartum dysglycemia (8). These numbers underline the importance of getting women to come back for the OGTT, so diabetes does not go undetected.

Going Forward

The WINGS tools have now been adapted, so they can be used in settings outside India. They are all

available at no charge from the IDF website: www.idf.org/women-and-diabetes/resource-centre.

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Diabetes in Pregnancy: My Experience

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I am honored to tell my story about being pregnant and having diabetes, and I am a bit overwhelmed by where to start. Living with type 1 diabetes can be somewhat of a chore on a daily basis, but add a few extra pounds and a whole lot of hormones and, wow, it sometimes feels like a full-time job! I am a registered nurse and I have had type 1 diabetes since I was 12 years old. I am now 41 and I have four beautiful healthy children. Although every single type 1 person is unique, here is my story.

I was administering multiple daily injections (and I mean multiple) during my first three pregnancies. As my little ball of joy grew in my tummy, I became increasingly hungry, and the hormones raging in my body were cause for numerous bolus injections as well as corrections. Although it is more work, it is possible to have a healthy pregnancy on multiple-dose injection (MDI) therapy, but I had developed significant lipohypertrophy from large doses of glargine. After my third child, my endocrinologist convinced me to consider pump therapy. I was opposed to the idea for a long time—"if it wasn't broke why fix it"—and I felt I was managing my diabetes fairly well. He asked me to consider a pump, stating not only is it the "gold standard" of diabetes care today, but it would allow me even better control and would be life changing. I was a huge skeptic; I did not want to be attached to something around the clock; the pump I would wear would label me, and everyone would know I have diabetes. And, more importantly, my colleagues at the hospital said "only brittle diabetics" wear insulin pumps.

Even so, I headed to Calgary and got myself trained on an insulin pump; the training itself was somewhat overwhelming and learning to trust my insulin administration to a device was very difficult. However, after my first few days using that pump, I knew it was awesome. I administered one needle every three days instead of 15; I could correct my blood sugar with small units of insulin to get me back to target; and I could have a snack whenever I wanted. I would input my current blood sugar, and of course, what I was eating, and the pump would calculate the dose I needed. This may be considered a disadvantage to insulin pump therapy as the training is intensive and requires frequent monitoring, but the advantage comes once you are competent and confident with its use.

I was very fortunate to have generous private insurance, which covered the $7000 insulin pump

Jodi Thorimbert and family.

in its entirety, including monthly supplies starting at $300/month. Today, people living with type 1 diabetes in Alberta are entitled to apply to the Alberta pump program, which covers the entire cost of the pump and the supplies if you qualify.

Diabetes in pregnancy requires much tighter targets, to avoid delivering the dreaded 12-pound child with complications; however, pump therapy allows us to achieve that goal so much easier than MDI. Throughout my last pregnancy, I was able to make changes to my insulin dosing immediately, because the pump only uses a rapid-analog insulin. I didn't have to wait for my next shot, and then troubleshoot how much to increase the Lantus or Levemir. In my first trimester, I was able to eat three meals comfortably, and then extend my meal bolus for delivery over a longer period of time. (My portions were larger, and the protein and fat content slowed down the carbohydrate absorption.) By the last trimester, I could only graze throughout the day, so if I ate 12 small meals, I just input what I was eating. Another perk from pump therapy is that it keeps track of your active insulin on board; this means we cannot stack our insulin when we bolus more than once in a four-hour period. My insulin requirements were tremendous in the last trimester (almost 200 units a day), and I had to change my pod every night. It was still a luxury to have such great control and just one needle a day.

My youngest child was born via a scheduled caesarean section (not due to any complication of diabetes), and I had a complete placenta previa. This meant surgery with an insulin pump. I worked closely with my endocrinologist to be able to keep my pump on throughout the surgery and successfully kept my blood glucose under 9 mmol/L. I was one of the first individuals permitted to keep my insulin pump on in the operating room and now more and more people are able to do the same as healthcare professionals grow accustomed to this patient-driven phenomenon. Insulin pump therapy allows us to have much more individual control than multiple daily insulin when we are always wondering if our insulin has peaked or if we have any active insulin still on board.

I have been very fortunate throughout child bearing and birth, both on MDI and pump therapy; however, if I knew then what I know now about pump therapy, there is no question I would have listened to my endocrinologist a long time ago. I have four happy healthy children; not one had any complications from diabetes in pregnancy. It is very possible that technology today is making living with diabetes so much easier; pumping gives us so much more freedom and better outcomes!

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Management of Diabetes Mellitus in Pregnancy

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Proper management of diabetes during pregnancy is essential to prevent complications to the mother and fetus, including perinatal mortality, congenital malformations, preterm delivery and neonatal morbidities (1). The Canadian Diabetes Association Clinical Practice Guidelines (CPGs) outline proper management for women with pre-gestational and gestational diabetes mellitus (GDM). Pregnant women should aim for tighter control of their blood glucose levels in order to reduce the risk of complications. Although targets should be individualized, the CPGs recommend aiming for a fasting plasma glucose less than 5.3 mmol/L; one-hour postprandial, less than 7.8 mmol/L; and two-hour postprandial, less than 6.7 mmol/L (1). To achieve these targets, insulin is the recommended therapy as it can help achieve glycemic control and is safe in pregnancy. However, intensive insulin regimens put patients at an increased risk of hypoglycemia. To reduce this risk, frequent blood glucose monitoring should be done—both pre- and postprandially (1).

Pre-Gestational Diabetes

In women with pre-gestational diabetes, a glycated hemoglobin (A1C) of less than seven per cent should be achieved prior to conception if possible (1). This reduces the risk of complications during pregnancy, and of hypoglycemia due to intensive insulin use (1). Three months preconception, women with pre-gestational diabetes should also be started on five milligrams of folic acid daily (which should be continued until at least 12 weeks post-conception) as this population has an increased risk of neural tube defects (1). At this time, any medications that are potentially embryopathic, such as angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers and statins, should be discontinued and noninsulin anti-hyperglycemics should be switched to insulin (1). Women with pre-gestational diabetes may use aspart or lispro instead of regular insulin to improve glycemic control and decrease hypoglycemia (2). Glargine and detemir may be used as an alternative to neutral protamine hagedorn (NPH) (2).Women with polycystic ovary syndrome can continue to use metformin; it may help to reduce the chance of spontaneous abortion, and can help ovulation induction (1,3-6). Postpartum, these women are at an increased risk of hypoglycemia, and should be closely monitored. These women are also at risk of thyroiditis, and should be screened at six to eight weeks postpartum with a thyroid-stimulating hormone test (2). Metformin and glyburide may be used during breastfeeding (2). Breastfeeding should be encouraged, especially in the incidence of maternal obesity, as it decreases the risk of child obesity (2).

Managing Diabetes During Pregnancy

Women diagnosed with diabetes during pregnancy can attempt to reach glycemic targets with lifestyle interventions alone. If diet is used to control blood glucose, ketones should be monitored, because this may put patients at a higher risk for starvation ketosis (1). Intensive insulin therapy should be initiated if targets are not met within two weeks (1).

Insulin

An intensive insulin regimen utilizing both basal and bolus insulin should be used as the best control of blood glucose levels (1,3-6). The rapid-acting analogues aspart and lispro are safe to use in pregnancy and may be preferable to regular insulin. They pose a lower risk of hypoglycemia and have more convenient dosing, although aspart shows no evidence of placental transfer and lispro only crosses the placenta at doses greater than 50 units (1,3-6). There is no evidence that aspart or lispro improves fetal outcome compared to regular insulin, but studies showed less hypoglycemia and improved A1C levels (1,2).

Similar to rapid-acting analogues, the long-acting analogues glargine and detemir pose less risk of hypoglycemia and are more conveniently dosed, compared to NPH. Detemir appears to be safe in pregnancy; however, there are no studies looking at placental transfer (2). A recent randomized controlled trial comparing detemir to NPH found no difference in maternal or fetal outcomes (2). There are no reports of adverse effects with the use of glargine; however, it can cross the placenta at large doses

(1,3-6). Data on glargine is more limited, and theoretical considerations make it less desirable (2). For these reasons, the use of detemir may be preferable to glargine. NPH has shown similar fetal and maternal outcomes to glargine and may be a good option for patients already stabilized on it (1).

Noninsulin Antihyperglycemics

Oral agents, such as glyburide and metformin, can be used in women who are non-adherent to insulin or who are unable, or refuse, to use insulin (1). Use of oral agents is off-label, and should be discussed with the patient (2). Women with type 2 diabetes, who are taking metformin or glyburide when they conceive, should continue until insulin is started (2) (Table 1).

The CPGs recommend glyburide and metformin as alternatives to insulin in women with GDM (1). Glyburide is effective in more than 80 per cent of patients with GDM (1). However, older women diagnosed earlier than 25 weeks who had higher glucose levels on their oral glucose tolerance test may not respond to glyburide (1). Although metformin does cross the placenta, its safety in pregnancy has been demonstrated in a number of studies (1,3-6). More information on the long-term safety of metformin in pregnancy will be available when results from the offspring follow up to the Metformin in Gestational Diabetes Trial are published (1).

Conclusion

Ideally, women with diabetes who are planning to conceive should begin preconception care at least three months prior to conception to optimize maternal and fetal outcomes (1). Achieving an A1C of less than seven per cent prior to conception will help to reduce maternal/fetal risks during pregnancy (1).

Table 1
Non-insulin antihyperglycemic agents in pregnancy

Drug	Pregnancy classification	Summary of evidence
Acarbose	B	• Very minimal systemic absorption. • Compared to insulin, there were no differences in pregnancy outcomes, but tolerance of acarbose was an issue (3-5).
Metformin	B	• Effective for improving ovulation and pregnancy rates in women with PCOS and may be beneficial in the first trimester of pregnancy to reduce the chance of spontaneous abortion. • One study showed no findings of abnormal growth or development in infants at 18 months when metformin was used during the full course of pregnancy, but more evidence is needed (3-6).
Meglitinides	C	• Use of repaglinide has shown adverse events in animal studies. • Use of repaglinide in one animal species during late pregnancy suggested effects on long bone growth, but no teratogenicity was observed (3-5,7).
Thiazolidinediones	C	• Found to cross the placenta in animal studies and one human study. • Rosiglitazone has shown increased risk of fetal adverse effects when used inadvertently in early pregnancy. • Rosiglitazone use was not associated with developmental toxicity in two case reports. • Pioglitazone has shown adverse effects in animal studies. In pregnant women, there are very few case reports of its use, and details regarding fetal outcome are limited (3-5,7).
Sulfonylureas	B/C	• Glyburide crosses the placenta. • If glyburide is used during pregnancy, it should be discontinued two weeks prior to the delivery date, as severe hypoglycemia lasting four to 10 days has been noted in infants born to mothers taking sulfonylureas at the time of delivery.

Table 1—continued
Non-insulin antihyperglycemic agents in pregnancy

Drug	Pregnancy classification	Summary of evidence
Sulfonylureas	B/C	• Additional adverse maternal and fetal events have been noted, and maybe influenced by maternal glycemic control or study design. • Use of gliclazide is contraindicated. • First-generation sulfonylureas (eg. chlorpropamide and tolbutamide) used in pregnancy were found to increase congenital abnormalities threefold if exposed during the period of organogenesis (3-5,7).
DPP-4 inhibitors	B	• Saxagliptin and linagliptin did not show adverse events in animal studies, except at doses that were maternally toxic. • In animal studies, adverse events have not been noted, and sitagliptin was found to cross the placenta (3-5,7).
Liraglutide	X	• No data available (3,4).
Exenatide	C	• No human data available. Adverse effects were observed in some animal reproduction studies. • One ex-vivo study showed that the fetal-to-maternal peptide concentrations were low, thus suggesting negligible exposure to the fetus. • Based on in vitro data, exenatide has low potential to cross the placenta. Avoid in pregnancy (3-5,7).
SGLT2 inhibitors	C	• No human data available. • Not recommended for use in pregnancy by manufacturer, especially during the second and third trimester. Shown to affect renal development in animal studies (3-5,7).

For pregnancy classifications, refer to reference 8. PCOS, polycystic ovary syndrome; SGLT2, sodium glucose link transporter 2.

Insulin is the drug of choice, because it gives the greatest glycemic control, is safe in pregnancy and is easy to modify (1). Women who are taking noninsulin antihyperglycemics should switch to an intensive insulin regimen (1). Women with GDM who are unable, or refuse, to use insulin can use metformin or glyburide as an alternative (1). However, these patients may have more challenges meeting more strict blood glucose targets used in pregnancy. If minor ailments occur during pregnancy, many nonprescription medications can be used safely. The use of any medication during pregnancy should be under the guidance of a healthcare professional.

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