CME

Controversies around gestational diabetes

Practical information for family doctors

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ABSTRACT

OBJECTIVE To summarize some of the issues facing primary care physicians who are seeing increasing numbers of patients with gestational diabetes mellitus (GDM) and to explore new developments in use of oral hypoglycemics during pregnancy.

QUALITY OF EVIDENCE All the literature on screening for GDM offers level III evidence. Much of the literature on treatment is also level III, but newer studies offer level I evidence and are more useful for daily practice. Existing research leaves many important questions unanswered; research findings are inconsistent among studies, and treatment strategies are challenging to implement.

MAIN MESSAGE Recent studies have clarified that rates of neonatal mortality and congenital malformations are not higher among the offspring of mothers with GDM. Treatment might affect birth weight, but whether treatment is associated with reductions in rates of shoulder dystocia and cesarean section is unclear. Several level I studies conclude that the oral hypoglycemic glyburide can be used safely and effectively during the second and third trimesters of pregnancy.

CONCLUSION Management of GDM remains a controversial area in obstetric care. It is a growing area of research, and new developments that might clarify risk and simplify treatment are expected in the coming years.

RÉSUMÉ

OBJECTIF Faire le point sur les questions qui confrontent le médecin de première ligne qui voit un nombre croissant de diabètes de grossesse (DG) et explorer les nouveaux développements dans l'utilisation des hypoglycémiants oraux chez la femme enceinte.

QUALITÉ DES PREUVES Toute les données publiées sur le dépistage du DG repose sur des preuves de niveau III. La majeure partie de la littérature sur le traitement est aussi de niveau III, mais certaines études récentes offrent des preuves de niveau I et sont plus utiles pour la pratique quotidienne. La recherche actuelle laisse plusieurs questions importantes sans réponse; certains résultats sont contradictoires et les stratégies de traitement proposées sont difficiles d'application.

PRINCIPAL MESSAGE Les études récentes ont montré clairement que les enfants des mères qui ont un DG n'ont pas un taux plus élevé de mortalité néonatale et de malformations congénitales. Le traitement pourrait modifier le poids à la naissance, mais on ignore s'il entraîne une réduction des taux de dystocie de l'épaule et de césarienne. Plusieurs études de niveau I concluent que l'hypoglycémiant oral glyburide peut être utilisé de façon sûre et efficace aux deuxième et troisième trimestre de grossesse.

CONCLUSION Dans le domaine des soins obstétricaux, le traitement du DG demeure un sujet controversé. Le nombre croissant d'études sur ce sujet permet d'espérer que de nouveaux développements viendront bientôt en clarifier les risques et en simplifier le traitement .

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Knowledge of gestational diabetes mellitus (GDM) is based on research that uses varying methods and reaches disparate conclusions. Many questions about diagnosis and management of GDM remain unanswered. The increasing prevalence of GDM in the coming years will pressure us to find practical answers to these questions.

Rural physicians and obstetricians dealing with large populations of aboriginal patients[1,2] and inner-city clinicians working with other ethnic groups that have a high prevalence of diabetes[3] are seeing type 2 diabetes in ever-younger people. Once a disease of older people, type 2 diabetes is now increasingly affecting women during their fertile years.[4,5] About 7% of pregnancies are complicated by diabetes; of these, about 90% are classified as GDM, 7% are previously diagnosed type 2 diabetes, and 4% are type 1 diabetes.[6] Many population studies indicate that the increasing incidence of GDM parallels that of its type 2 cousin.[7-10] In some aboriginal populations, GDM is twice as prevalent as among nonaboriginal people.[8]

Family physicians attending 20 to 40 deliveries a year see about two or three patients who have been diagnosed with GDM as a result of screening and diagnostic testing. We hope this literature review and synthesis will help clinicians better understand the controversies surrounding GDM and how existing research can best inform management.

Quality of evidence

MEDLINE was searched from January 1966 to December 2004 using the MeSH headings diabetes mellitus, gestational, non–insulin-dependent, pregnancy, metformin, sulfonylurea compounds, glyburide, guidelines, and polycystic ovary syndrome. In addition, guidelines of the Society of Obstetricians and Gynaecologists of Canada (SOGC),[11] the 2003 Canadian Diabetes Association Clinical Practice Guidelines,[5] and the 2003 guidelines of the American Diabetes Association[10] and their references were examined. Guidelines for screening and treatment are based mostly on level III evidence. Research to date provides poor-quality evidence based on retrospective chart reviews and case reports, but larger prospective studies are now under way. Most of the literature reviewed was level II and III evidence. Level I evidence began to appear in the 1990s.

What is GDM?

Gestational diabetes mellitus is diabetes arising, or first diagnosed, during pregnancy.[5] Many clinicians assume the definition includes only those diagnosed by a common screening process at 24 to 28 weeks' gestation, but in fact it encompasses any type of diabetes first diagnosed during pregnancy. For example, it includes "occult" type 2 diabetes, which is recognized for the first time during pregnancy. The fact that the definition can include different patient populations could explain some of the variation in research results with regard to pregnancy outcomes.

Gestational diabetes classically presents in the third trimester as the placenta matures and placental hormones contribute an insulin resistance that usually recedes after the placenta is delivered.[12,13] Glucose crosses the placenta and stimulates fetal insulin production; maternal or exogenous insulin does not.

Since many patients with GDM go on to develop overt type 2 diabetes[14,15] and both diseases are characterized by insulin resistance,[12] some authors postulate that they represent points on a continuum of glucose intolerance.[7,16,17] Poor outcomes sometimes result from undiagnosed type 2 diabetes and first-trimester exposure to hyperglycemia.[18] Until further research is available, most opinions are unsupported by adequate evidence. In 2004, the Cochrane Library found no evidence that screening or treatment made an appreciable difference in perinatal outcomes.[19]

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This leads some clinicians to challenge the existence of GDM.[20] Family physicians and their patients need to be aware that there is a great deal of uncertainty about this.

Screening

Screening is routine but not universal in Canada. Some centres neither screen nor treat GDM.[21] All screening guidelines are based on level III evidence. Since obstetrics is a high-risk part of practice, it makes sense that, until GDM is universally declared benign, we need to screen and treat within the regional peer and consultant environment in which we practise.

In the United States, 96% of obstetricians universally screen pregnant patients for diabetes.[22] In the United Kingdom, 17% screen universally and 72% screen if other risk factors exist.[23] The SOGC guidelines recommend routine screening at 24 to 28 weeks, unless patients are low risk (younger than 25 years, body mass index [BMI] less than 27, and no personal, family, or ethnic history of diabetes mellitus).[11] The American Diabetes Association has similar standards.[10] The Canadian Diabetes Association and the American College of Obstetricians and Gynecologists recommend universal screening.[5,24] Most agencies, including the SOGC, encourage screening high-risk patients (≥35 years; BMI greater than 30; polycystic ovary syndrome [PCOS]; acanthosis nigricans; corticosteroid use; and personal, family, or ethnic history of DM) at the first prenatal visit.[11]

A 50-g nonfasting 1-hour glucose challenge is normal if results are <7.8 mmol/L and diagnostic if they are ≥10.3 mmol/L. Values in between require a 75-g oral glucose tolerance test with measurements taken fasting and at 1 hour and 2 hours after a meal. If two of three values exceed the norm (fasting ≥5.3; 1 hour ≥10.6; 2 hour ≥8.9), GDM is also diagnosed. This approach has 80% sensitivity and 85% specificity.[11] Fasting glucose tests have similar sensitivity (80%) but a high false-positive rate (57% specificity).[25] Screening in Canada is routinely done with a nonfasting 50-g challenge at 24 to 28 weeks' gestation.[11]

How does GDM affect pregnancy?

Organogenesis. Organogenesis is generally thought to start in the third week after fertilization and to be completed by 8 or 10 weeks' gestation. Women whose periods are 2 weeks late are 3 weeks postfertilization and postimplantation and are considered to be at 6 weeks' gestation. By the time most women are aware they are pregnant, substantial organogenesis has occurred. Certainly many first prenatal visits fall after the 10-week mark, and undiagnosed "occult" type 2 diabetes might have already had a role in pregnancy outcome. We know that periconceptual hyperglycemia is teratogenic.[13,15,26-28]

Maternal insulin does not cross the placenta, and fetal beta cells do not produce insulin until about 12 weeks' gestation.[6] Early hyperglycemia (especially HbA_{Ic} >7.5%)[29] can lead to congenital malformations and miscarriages, which are two to three times more likely among patients with type 1 and type 2 diabetes. Good preconception glycemic control is important. Current evidence shows no effect of GDM on organogenesis.

Macrosomia. Although macrosomia has been defined as birth weight of both >4500 g and >4000 g, most studies use >4000 g.[30,31] Recent literature defines macrosomia as identical to large-for-gestational-age (LGA), which is size >90th percentile for gestational age.[32,33] Some ethnic groups have an inherent tendency toward macrosomia (level II evidence).[8]

When a fetus is exposed to high levels of maternal glucose, it responds by producing higher levels of insulin in its circulation. Since insulin has many growth hormone properties,[16,32] the result is fetal macrosomia and an increased rate of cesarean section (level II evidence).[31]

Macrosomic and LGA infants are born in 12% of deliveries in the general population[32] and in about 20% of deliveries involving GDM.[31] Established risk factors for macrosomia include maternal glycemic levels (level II evidence),[34-36] maternal prepregnancy weight (level II evidence),[24,37] maternal age over 40 (level II evidence),[38] and aboriginal ethnicity (level II evidence).[8] That said, most macrosomic infants arrive with no identifiable maternal risk factors,[32] and GDM predicts less than 5% of macrosomia.

The association between macrosomia and maternal glycemic levels holds both for existing type 2 diabetes (odds ratio [OR] 6.96) and for GDM (OR 2.77) (level II evidence).[38] Postprandial hyperglycemic levels seem to predict macrosomia best (level II evidence).[39]

Interesting to note is a diagnosis effect. Labeling a patient with GDM increases the likelihood that she will have a cesarean section (level I evidence).[40] Limiting the criteria for cesarean sections to maternal glycemic levels and ultrasound estimates of fetal size can reduce the intervention rate to that in the general population (level I evidence).[41] The Toronto Tri-Hospital GDM Project demonstrated decreased rates of macrosomia but not cesarean section, which further suggests that GDM labeling affects the rate of surgical intervention.[42] Some study protocols call for elective cesarean sections when a given ultrasound-estimated birth weight is reached, further contributing to the research association between macrosomia and cesarean sections.

In 2004, the Cochrane Library reviewed three studies (223 patients) and found GDM treatment was associated with a non-significant risk reduction (RR) for macrosomia (RR 0.55, 95% confidence interval [CI] 0.19 to 1.61) and cesarean section (RR 0.86, 95% CI 0.51 to 1.45).[20] Ontario birth statistics from 1984 to 1996 demonstrated no change in rates of macrosomia or cesarean section in areas that stopped routine screening for GDM (level II evidence).[21] This suggests that screening artificially increases disease prevalence with no change in outcome. In most research studies of GDM, cesarean section rates are about 30%.[31,42]

Neonatal hypoglycemia. Postpartum neonatal hypoglycemia might occur when neonates are no longer exposed to high levels of maternal glucose. At delivery, neonates continue to produce high levels of insulin, but withdrawal of high concentrations of maternal glucose might lead to relative neonatal hyperinsulinemia and subsequent hypoglycemia and the requirement for a glucose infusion after delivery. Prolonged neonatal hypoglycemia was seen in experiments with first-generation sulfonylureas in the 1970s and is still encountered in some patients treated with insulin (up to 4% of neonates whose mothers are taking insulin could require glucose infusion) (level II evidence).[32]

Congenital malformations. Congenital abnormalities (3% incidence in total population[32]) are not found more frequently in the offspring of patients with GDM (level I evidence),[31,43] but they are in the offspring of patients with both type 1 and type 2 diabetes (level II evidence).[7,18,30,32] A recent prospective study of 2400 pregnant diabetic women in New Zealand found the rate of congenital abnormalities among GDM patients was 1.4%, among type 2 diabetic patients was 4.4%, and among type 1 diabetic patients was 4.6% (level II evidence).[7]

Perinatal mortality. Perinatal mortality (stillbirth and neonatal death in the first week post partum) is mentioned in the GDM literature, but with lessening frequency from the 1970s on. Current accepted wisdom is that the rate is similar to that observed in the general population (0.77% in Canada[44]).[32] Whether this is due to diabetic treatment or to better general obstetric care is unclear.[45]

Estimates of perinatal mortality associated with GDM have varied greatly over the past decades. A small study by O'Sullivan and associates in 1973 demonstrated a fourfold increase in perinatal mortality among offspring of women with GDM (level II evidence).[46] The study had several methodologic discrepancies: some patients were unaccounted for, it was not randomized, not all variables were controlled for, and subjects were not matched with controls. Interestingly, it was the last time insulin treatment was compared with no treatment for GDM, and it found no significant effect of treatment. Even so, the study strongly supported the view that GDM was pathologic and required insulin treatment. The authors also postulated that "some factors other than intolerance to glucose are required" for the detrimental effects they documented, likely age and prepregnancy maternal weight. No adverse effects were found in the offspring of thin young women (<30 years) with GDM.

Twenty years later, Langer and colleagues carried out a prospective, partially randomized intervention in 2500 women with GDM (level II evidence).[31] They

compared conventional (and suboptimal) insulin control with more intensive monitoring and treatment. Both groups had lower perinatal mortality rates than 4922 controls without GDM.

Treatment

Insulin. The standard approach[5] to treatment of GDM in North America and Europe is insulin therapy for patients who cannot get glycemic control through diet and exercise regimens. Most patients (60% to 95%) can be managed with diet alone (level II evidence).[47-49] Primary care clinicians might not be able to reproduce suggested "intensive" insulin treatment in their practices. Such treatment can include insulin injections up to four times daily and home glucometer readings seven times daily.[30] Compliance with glucometer testing is less than 60% even in well supported research studies.[31,49]

Although insulin is a large molecule that does not cross the placenta, it can be transported as part of an antibody-insulin complex.[6] An autoimmune reaction to exogenous insulin treatment could also affect the growth of a fetus.[50]

In 1994, Langer and colleagues followed 2450 largely Hispanic women with GDM who were randomized to conventional treatment or intensified monitoring with twice-daily insulin therapy. These women were compared with 4922 controls without GDM (level I evidence).[31] The intensively managed group monitored their glucose levels at home seven times daily and had similar outcomes to the control group. The conventional group monitored their glucose only four times daily and had significantly higher rates of cesarean section and macrosomia. Intensive monitoring led to patients taking higher doses of insulin (up to 90 U/d) and having lower rates of macrosomia and cesarean section. The clinical drawback to this study was the 20% incidence of hypoglycemia attacks in the intensively treated group. In contrast, the 1998 Toronto Tri-Hospital Gestational Diabetes Project found a decrease in the rate of macrosomia but not in the rate of cesarean sections when it studied 145 intensively treated women (level I evidence).[42]

Insulin has commonly been administered in twice-daily split doses at a starting dose of 8N/4R in the morning and 4N/4R in the afternoon. Insulin lispro can be safely used to replace regular insulin.[51] A recent study comparing this traditional administration to four times daily dosing at a common starting dose of 4R with meals and 4N at bedtime found no difference in rates of cesarean section, macrosomia, shoulder dystocia, preterm delivery, or neonatal hypoglycemia (level I evidence).[52] It did find a high rate of maternal hypoglycemic events (17%) during intensive treatment; the only benefit was lower incidence of neonatal jaundice and neonatal hypoglycemia. Four times daily dosing might be useful for patients with erratic mealtimes.

There is not much evidence to prefer four times daily over twice-daily insulin regimens. Primary care physicians need to balance compliance and side effect management with the intensity of GDM treatment. Fasting values of <5.3 mmol/L and values 1 hour after meals of <7.8 mmol/L are accepted treatment targets.[5]

Glyburide. Early studies of first-generation sulfonylureas showed that they crossed the placenta in substantial quantities and were associated with postpartum neonatal hypoglycemia.[53] In 1994, placental testing demonstrated that glyburide, a second-generation sulfonylurea, did not cross the placenta.[43] Glyburide's high molecular weight and other chemical properties[54-56] gave authorities the confidence to approve it for clinical trials of treating GDM. In 2000, Langer showed that most of 400 randomized subjects with GDM achieved appropriate glycemic control with glyburide.[53] When treated in the second and third trimesters (beginning at 11 weeks' gestation), their outcomes were similar to those randomized to insulin treatment, and there was no risk to mother or fetus (level I evidence).[53] These studies have allowed the Canadian and American diabetes associations to acknowledge that glyburide could be considered for treatment of GDM, if necessary, during the second and third trimesters of pregnancy. In research settings, most women choose oral hypoglycemic therapy over insulin therapy.[57]

A recent prospective cohort study of 75 patients with GDM in Texas and a randomized

controlled trial of 200 similar patients in Florida investigated glyburide as a first-line treatment for the 40% of women who do not achieve glycemic control through exercise and diet.[58,59] Both studies found that more than 80% of women treated with glyburide achieved glycemic control (most with ≤7.5 mg/d) and had excellent outcomes of pregnancy (level I and II evidence). A 2004 survey of 1400 American obstetricians indicated that 13% of them now begin GDM treatment with glyburide when diet and exercise fail.[22]

Metformin. Studies of placental transportation of metformin and umbilical cord analyses in metformin-treated patients have not been done recently. A report in the 1960s demonstrated that metformin did not cross the placenta.[60] We hope metformin can be submitted to more modern testing as glyburide has been. The United States Food and Drug Administration considers it a Class B drug (animal studies show no ill effects). Metformin's safety during pregnancy is suggested by studies where it is used to treat infertility in patients with PCOS (level I evidence),[61] which is also associated with insulin resistance.[62] A study by Glueck and coworkers showed that metformin significantly reduced the incidence of first-trimester loss among women with PCOS (level I evidence).[63] Metformin was used initially for 4 to 6 months to promote ovulatory cycles and to treat infertility.[62] Nondiabetic women with PCOS treated preconceptually and *throughout pregnancy* with metformin (2.5 g/d) had a 10-fold lower incidence of GDM (31% to 3% and produced healthy, normal infants.[61,64,65]

We need a well designed trial of metformin to determine whether it is safe for GDM patients in pregnancy. Evidence in women with PCOS and results of some trials in South Africa are interesting.[66] A 2004 review of 23 metformin studies suggested that metformin might be used to achieve euglycemia in some patients during pregnancy[67] (level III evidence).

Ongoing research

No randomized controlled trials have focused on use of oral hypoglycemics during organogenesis during the first trimester. Particularly vexing is most studies' inability to differentiate between a first-trimester hyperglycemic effect, a known teratogen, and any medication effect.

Future research on management later in pregnancy looks exciting. Use of metformin for GDM at 24 weeks' gestation has been successfully pilot-tested in 30 Australian women randomized to metformin or insulin. Perinatal outcomes were similar. A larger trial has begun.[68]

The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study, a 5-year prospective observation of 25 000 women in 10 countries using a 75-g glucose tolerance test at 24 to 32 weeks' gestation will look at maternal health and neonatal outcomes, including macrosomia, neonatal hypoglycemia, cesarean delivery, and fetal hyperinsulinism.[33] We hope this large study will answer some questions about maternal glycemia that is "less severe than overt diabetes."[33]

Bottom line

- Screening programs balance cost, outcomes, and disease incidence to decide who and when to investigate. Identifying patients with simple GDM at 24 to 28 weeks might allow us to lower rates of macrosomia and perhaps cesarean section, but that might be all.
- Although not currently recommended by Canadian or American diabetes associations, new literature (albeit on trials involving women with PCOS) suggests that metformin is safe and beneficial during the first trimester.[61,63-65]
- Level I evidence indicates that patients with GDM identified in the second and third trimesters can safely achieve acceptable glycemic control with glyburide.[21,58,59]
- Insulin remains the common treatment for GDM because it appears safe and achieves glycemic control (level I evidence), whether used two or four times a day.[11]

- We hope the anticipated HAPO study[33] will inform us about relevant targets and outcomes with regard to GDM.

Conclusion

Clinicians in primary care need the research community to resolve some of the practical issues regarding our approach to and understanding of GDM. In the meantime, less complicated treatment options, such as glyburide, are welcome additions to insulin therapy. As our knowledge grows, we need to translate it into attainable strategies for our patients and our practices.

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EDITOR'S KEY POINTS

- There is considerable controversy as to whether screening and treating gestational diabetes mellitus (GDM) makes an appreciable difference in perinatal outcomes.
- Gestational diabetes appears to contribute to macrosomia; treatment of GDM lowers rates of macrosomia, but not rates of cesarean section. Rates of cesarean section are increased by labeling patients with GDM. Recent evidence suggests that congenital abnormalities and perinatal mortality are not more common among the offspring of patients with GDM.
- Conventional treatment has been with diet, exercise, and addition of insulin. There is emerging evidence that oral hypoglycemics are safe and effective.

POINTS DE REPÈRE DU RÉDACTEUR

- La question de savoir si le dépistage et le traitement du diabète de grossesse (DG) changent quelque chose à l'issue périnatale est fort controversée.
- Le diabète de grossesse semble augmenter le taux de macrosomie; le traitement du DG diminue ce taux mais non celui des césariennes. La patiente chez qui on pose un diagnostic de DG risque davantage d'avoir une césarienne. Les données récentes indiquent que les taux de malformations congénitales et de mortalité périnatale ne sont pas augmentés lorsque la mère présente un DG.
- Le traitement traditionnel incluait régime, exercice et ajout d'insuline. Les données récentes laissent croire que les hypoglycémiants oraux sont sûrs et efficaces.

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