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Preconception management of diabetes

The risk of adverse pregnancy outcomes in women with type 1 or type 2 diabetes can be reduced with preparation that includes improving glycemic control and discontinuing antihypertensive agents prior to conception.

ABSTRACT: Women with type 1 or type 2 pregestational diabetes have an increased risk of adverse pregnancy outcomes when compared with the general maternal population. The risks to offspring include a greater than threefold increase in congenital heart disease, a greater than fourfold increase in neural tube defects, and a nearly fourfold increase in perinatal death. These risks to offspring and the risk of maternal retinopathy and nephropathy can be attributed primarily to the negative impact of hyperglycemia. To ensure the safest possible conditions for pregnancy, women with diabetes should receive preconception care. Although some aspects of preconception care will depend on whether a patient has type 1 or type 2 diabetes, the general management principles are the same for both. Patients should be encouraged to meet glycated hemoglobin targets, should be assessed for retinopathy, and should be screened for nephropathy. They should also be advised to take folic acid supplements and discontinue the use of antihypertensive agents and statins.

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It is well known that women with type 1 or type 2 pregestational diabetes have an increased risk of adverse pregnancy outcomes. One study comparing the offspring of women in the general population and offspring of women with diabetes found a greater than threefold increase in congenital heart disease, a greater than fourfold increase in neural tube defects, and a nearly fourfold increase in perinatal death.[1] These increases in risk can be attributed primarily to the negative impact of hyperglycemia on early fetal development and point to the need for medical care prior to conception.

Preconception care should focus not only on helping patients achieve better glycemic control, but also on optimizing the pharmacological means used to achieve glycemic targets, monitoring for progression of retinopathy, screening for nephropathy, and discontinuing medications that may affect fetal development. Until optimal conditions for pregnancy are established, women should be encouraged to use contraception.

Improving glycemic control

High glycated hemoglobin (HbA1c) values are strongly correlated with adverse pregnancy outcomes,[2,3] and patients are therefore encouraged to reach an HbA1c target of 7.0% or less before pregnancy, with a target of 6.5% or less being preferable if this level can be achieved safely without undue risk of hypoglycemia.[4] Above 7.0%, adverse outcomes increase by approximately 5.5% for every 1.0% in HbA1c.[3]

Comprehensive preconception care is associated with major reductions in adverse pregnancy outcomes.[5,6] Unfortunately, a recent survey of pregnant women with diabetes in Ontario found that a disappointingly low

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proportion of women with pregestational diabetes reported a high degree of effort in planning their pregnancy (47%) and optimizing glycemic control (58%).[7] Physicians must be proactive in educating their reproductive-age patients living with diabetes about the importance of pregnancy planning, the risks of forgoing preconception care, and the need to consult with medical practitioners prior to conception. Referral to a diabetes in pregnancy clinic may be considered.

Oral hypoglycemic agents

Most patients presenting with type 2 diabetes before pregnancy will be managed on oral hypoglycemic agents (OHAs). Decisive conclusions on the safety of OHAs have yet to be reached, as individual studies have been small or of poor quality and have reported conflicting results, or have failed to account for important confounding factors.[8,9] However, despite study heterogeneity, one meta-analysis of first-trimester exposure to various OHAs, including metformin, glyburide (one study), and glipizide (two studies), reported no increase in rates of major congenital malformation.[8] Similarly, a second meta-analysis focusing on first-trimester exposure to metformin showed no increased risk of major congenital anomalies.[9] Finally, a prospective database study comparing fetal outcomes among women with type 2 diabetes treated with diet, insulin, or sulfonylureas (chlorpropamide, glyburide, glipizide) in the first trimester found no significant difference in the incidence of major or minor congenital anomalies in the three treatment groups.[10]

The safety of newer OHAs such as dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose linked transporter 2 (SGLT2) inhibitors, and injectable glucagon-like peptide-1 (GLP-1) receptor agonists has not been explored adequately for pregnancy. Any data on the safety of these agents during pregnancy are from animal studies, as detailed in product monographs. Animal studies of DPP-4 inhibitors demonstrate a small increase in skeletal malformations, delayed skeletal ossification, or both, at extreme supratherapeutic doses of sitagliptin,[11] saxagliptin,[12] and linagliptin.[13] Additionally, linagliptin use in rats and rabbits was associated with reduced fetal weight and intrauterine death at extreme supratherapeutic doses. Animal studies of SGLT-2 inhibitors (dapagliflozin, canagliflozin, enpagliflozin) show potential defects in fetal renal development.[14] Regarding GLP-1 receptor agonists studied in a rat model, exposure to exenatide was associated with slowed fetal growth, skeletal defects, and perinatal mortality at extreme supratherapeutic doses,[15] while exposure to liraglutide was associated with increased incidence of miscarriage at supratherapeutic doses. In a rabbit model, the risk of major congenital anomalies was found even at subtherapeutic doses.[16]

We recommend DPP-4 inhibitors, SGLT2 inhibitors, and GLP-1 receptor agonists be stopped when pregnancy is confirmed and that every effort be made to start insulin therapy as quickly as possible. Ideally, physicians should transition patients with type 2 diabetes to insulin therapy prior to conception. However, if patients on metformin and/or sulfonylurea present with an unplanned pregnancy, they should continue on these agents until insulin can be introduced and titrated. Given the known teratogenic effect of hyperglycemia in the first trimester, it is possible that stopping these medications prematurely could cause more harm than benefit. This recommendation is also in accordance with the Canadian Diabetes Association guidelines.[4]

Insulin

Intensive insulin therapy, either by basal-bolus injection or continuous subcutaneous insulin infusion, is the recommended method of achieving the necessary preconception glycemic targets.[4] While patients with type 1 diabetes will already be managed on insulin, most patients with type 2 diabetes will need to be transitioned to insulin prior to conception.

In addition to human regular insulin (Novolin ge Toronto or Humulin R), two rapid-acting insulin analogs appear safe for use during pregnancy. A prospective observational study comparing insulin lispro (Humalog) and regular insulin,[17] and a randomized controlled trial of insulin aspart (NovoRapid) and regular insulin[18] showed no differences in major fetal outcomes such as congenital malformations, perinatal mortality, or macrosomia. In addition, the study examining lispro found no increased rate of preeclampsia,[17] while aspart was shown to result in a lower occurrence of preterm delivery (20.3% vs 30.6% with regular insulin).[18] Both insulin analogs were found to be noninferior to regular insulin in terms of maternal outcomes; women taking lispro had a lower HbA1c throughout gestation,[17] while women on aspart reported a nonsignificant reduction in hypoglycemic events.[19] No pregnancy data are currently available for insulin glulisine (Apidra).

Concerning basal insulin, a randomized controlled trial comparing insulin detemir (Levemir) and insulin NPH showed detemir was safe to use in pregnancy, with no significant difference in the rates of congenital malformations and other adverse perinatal events.[20] Detemir also demonstrated noninferiority in observed maternal outcomes such as HbA1c and hypoglycemia.[21] Pregnancy safety data regarding insulin glargine (Lantus) are

limited to findings from observational cohort studies. Some concerns have been raised regarding glargine use in pregnancy because of the product's greater affinity for the insulin-like growth factor receptor[22] and potential to affect fetal growth and development. However, in a meta-analysis of studies comparing pregnancy outcomes of insulin glargine users and insulin NPH users, no concerning trends emerged with key fetal outcomes, including congenital anomalies and macrosomia.[23] Furthermore, it was determined that glargine does not cross the placenta to a detectable degree at therapeutic doses.[24] Therefore, while a discussion regarding the limited evidence of safety for insulin glargine in pregnancy is warranted in the preconception stage, it is quite reasonable for women established on glargine to consider ongoing use in pregnancy.

Managing retinopathy

A subanalysis of the landmark Diabetes Control and Complications Trial (DCCT) examined the effect of pregnancy on the development and progression of retinopathy among women with type 1 diabetes.[25] This analysis showed that pregnancy appears to independently increase the risk of short-term progression of retinopathy from conception up to 1 year postpartum, but does not affect long-term retinopathy outcomes.[25] Retinopathy progression during pregnancy has been subsequently observed in other studies of women with type 1 diabetes[26] and those with type 2 diabetes.[27] Individuals with more advanced retinopathy and poor glycemic control at pregnancy outset appear at higher risk for retinopathy progression.[25,26] In women with poor baseline glycemic control, rapid HbA1c reductions upon the institution of strict glycemic control for pregnancy may also contribute to retinopathy progression.[25,26]

Preconception care for patients with diabetes

- Encourage patients to meet HbA1c target of ≤ 7.0%.
- Refer patients to a diabetes in pregnancy clinic for preconception care if necessary.
- If patients with type 2 diabetes are taking oral hypoglycemic agents, transition them to insulin.
- Refer patients for ophthalmologic assessment prior to conception and in the first trimester.
- Screen patients for nephropathy and counsel patients at risk.
- Recommend patients take 1.0 mg of folic acid daily starting 3 months before pregnancy.
- Advise patients to discontinue use of ACE inhibitors, ARBs, and statins.

All women with diabetes should have ophthalmologic assessments prior to conception and during the first trimester. Additional monitoring for microvascular complications during pregnancy and postpartum may be needed and is at the discretion of ophthalmology.[4]

Managing nephropathy

Women with diabetic nephropathy are a high-risk subgroup for maternal and fetal pregnancy complications, and all women with diabetes should undergo preconception screening for nephropathy. A study comparing pregnancy outcomes of women with normal urinary albumin excretion (below 30 mg/24 h) and women with microalbuminuria (30 to 300 mg/24 h) found significantly different incidence rates for preterm delivery in the two groups (35% vs 62%), mostly owing to an increased incidence of preeclampsia (6% vs 42%).[28] The risk of these complications was higher still in the subset of women with baseline proteinuria in the overt nephropathy range (above 300 mg/24 h), even with preserved renal function.[28] In a more recent study, an intensified antihypertensive strategy was found to improve obstetrical outcomes in women with microalbuminuria to such a degree that preeclampsia was averted and the incidence of preterm delivery was reduced to that observed in women with normal urinary albumin excretion.[29] Obstetrical outcomes were also improved in women with more pronounced proteinuria, but to a lesser extent.[29]

Reviewing renal outcomes, it appears that maternal serum creatinine rather than proteinuria determines maternal renal function following pregnancy. In a case-control study of renal function decline in a cohort of women with type 1 diabetes, patients with overt nephropathy but normal creatinine concentration showed no detrimental effect as a result of pregnancy.[30] In contrast, women with moderate-to-severe renal insufficiency, defined as a serum creatinine concentration of 124 μmol/L or higher prior to conception or early in pregnancy, experienced significant and permanent deterioration in renal function as a result of pregnancy.[31,32] In a cohort of 11 pregnant women with this degree of renal impairment specifically due to diabetic nephropathy, 5 experienced irreversible pregnancy-related renal damage and required dialysis within approximately 2 years of delivery.[32] In this same cohort, perinatal survival was 100%, but the

very high rate of premature delivery (79%) resulted in significant neonatal morbidity.[32]

Women with any degree of diabetic nephropathy should be counseled on their increased risk of adverse fetal outcomes, and those women with more advanced diabetic nephropathy and reduced renal function should be counseled on the possibility of permanent deterioration of renal function as a result of pregnancy.

Additional management considerations

As well as improving glycemic control and managing common complications of diabetes before pregnancy, patients should be advised about folate needs and medications that may affect fetal development.

Folate

Ensuring adequate folate intake before pregnancy is known to lower the incidence of congenital anomalies, particularly neural tube defects. Women with pregestational diabetes should add folate-rich foods to their diet (leafy greens, peas, lentils, oranges) and take a folic acid supplement (1.0 mg) daily for at least 3 months prior to conception.[33]

Antinhypertensive agents and statins

Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are commonly prescribed for the treatment of hypertension in women with diabetes, and deserve special consideration at the preconception stage. Conflicting evidence exists regarding the fetal risks of first-trimester exposure to these agents. A large database study found that first-trimester exposure to ACE inhibitors was associated with an increased risk of major congenital malformations, primarily in the cardiovascular and central nervous systems,[34] but women with diabetes were excluded from the analysis to reduce the risk of hyperglycemia as a confounding variable. Conversely, a meta-analysis found that infants born to women taking ACE inhibitors or ARBs in the first trimester did not have increased risk of congenital anomalies when compared with infants exposed to all other antihypertensive agents.[35] However, in this trial it was noted that maternal treatment for hypertension overall was associated with an increased risk, possibly due to the confounding factors of advanced maternal age, weight, and hyperglycemia.[35] Regardless of their safety in the first trimester, ACE inhibitors and ARBs are associated with clear negative fetal outcomes in the second and third trimesters, including fetal renal failure, anuria, and death,[36] and these medications should be stopped upon confirmation of pregnancy.

All statins are contraindicated for use during pregnancy. Statin therapy should be discontinued prior to conception because of limited evidence that fetal exposure in the first trimester increases the risk of congenital malformations.[37]

Summary

Successful pregnancies for women with type 1 or type 2 pregestational diabetes require planning and optimization of glycemic control. Patients with type 2 diabetes will, ideally, transition from oral hypoglycemic agents to insulin prior to conception, and women with type 1 or type 2 diabetes will have ophthalmologic assessment and be screened for nephropathy. In addition, women with diabetes should begin folic acid supplementation and discontinue use of antihypertensive agents and statins in preparation for conception. Primary care and specialist physicians alike should be prepared to counsel women with diabetes on preconception issues to reduce the risk of adverse outcomes. BCMJ

Competing interests

None declared.

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