Teratogenicity Associated With Pre-Existing and Gestational Diabetes

This guideline has been reviewed by the Genetics Committee and the Maternal Fetal Medicine Committee, and approved by the Executive and Council of the Society of Obstetricians and Gynaecologists of Canada

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Abstract

Objective: To review the teratogenesis associated with pre-existing and gestational diabetes, to provide guidelines to optimize prevention and diagnosis of fetal abnormalities in women with diabetes, and to identify areas specific to fetal abnormalities and diabetes requiring further research.

Options: Pre-conception counselling, pre-conception and first trimester folic acid supplementation, and glycemic control.

Outcomes: Increased awareness of fetal abnormalities associated with pre-existing and gestational diabetes.

Evidence: The Cochrane Library and Medline were searched for English-language articles, published from 1990 to February 2005, relating to pre-existing and gestational diabetes and fetal abnormalities. Search terms included pregnancy, diabetes mellitus, pre-existing diabetes, type 1 diabetes, type 2 diabetes, insulin dependent diabetes, gestational diabetes, impaired glucose tolerance, congenital anomalies, malformations, and stillbirth. Additional publications were identified from the bibliographies of these articles as well as the Science Citation Index. All study types were reviewed. Randomized controlled trials were considered evidence of the highest quality, followed by cohort studies. Key studies and supporting data for each recommendation are summarized with evaluative comments and referenced.

Values: The evidence collected was reviewed by the Genetics and Maternal Fetal Medicine Committees of the Society of Obstetricians and Gynaecologists of Canada (SOGC) and quantified using the criteria and classifications of the Canadian Task Force on Preventive Health Care.

Recommendations

1. Experimental studies suggest that hyperglycemia is the major teratogen in diabetic pregnancies, but other diabetes-related factors may also affect fetal outcomes. Further research using animal models is required to clarify the teratogenic factors associated with pre-existing and gestational diabetes. (II-3C)

2. Prospective and retrospective cohort studies have demonstrated an increased risk of congenital abnormalities with pre-existing diabetes. Further studies that include outcomes from first and second trimester pregnancy terminations, account for potential confounding variables, and use appropriate control groups are required. (II-2A)

3. Prospective and retrospective cohort studies have demonstrated an increased risk of congenital abnormalities with gestational diabetes. This observation is probably related to the inclusion of

Table 1. Key to evidence statements and grading of recommendations, using the ranking of the Canadian Task Force on Preventive Health Care

Quality of Evidence Assessment*	Classification of Recommendations†
I: Evidence obtained from at least one properly randomized controlled trial	A. There is good evidence to recommend the clinical preventive action
II-1: Evidence from well-designed controlled trials without randomization	B. There is fair evidence to recommend the clinical preventive action
II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group	C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making
II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category	D. There is fair evidence to recommend against the clinical preventive action
	E. There is good evidence to recommend against the clinical preventive action
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	I. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making

∗The quality of evidence reported in these guidelines has been adapted from The Evaluation of Evidence criteria described in the Canadian Task Force on Preventive Health Care.[4]
†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the The Canadian Task Force on Preventive Health Care.[4]

women with unrecognized type 2 diabetes. Clarification of the relationship between gestational diabetes and congenital abnormalities by studies that include outcomes from first and second trimester pregnancy terminations, account for potential confounding variables, and use appropriate control groups are required. (II-2A)

4. In some women, type 2 diabetes may be identified for the first time in pregnancy. Pre-conception recognition of women at high risk for type 2 diabetes and optimal glycemic control may reduce the risk of congenital anomalies. (II-2A)

5. Second generation sulfonylureas have not been associated with congenital abnormalities in human studies. The use of biguanides may be associated with other adverse perinatal outcomes. The use of other oral antihyperglycemic agents is not recommended in pregnancy. (II-2A)

6. The risk of congenital anomalies is increased in the offspring of obese women with diabetes. A healthy diet and regular exercise may help optimize pre-pregnancy weight and reduce the risk of congenital anomalies. (II-2A)

7. Accurate determination of gestational age is required in women with diabetes. Given the increased risk of congenital abnormalities, they should be offered appropriate biochemical and ultrasonographic screening and a detailed evaluation of fetal cardiac structures. (II-2A)

8. Women with diabetes should be offered pre-conception counselling with a multidisciplinary team to optimize general health and glycemic control and to review the risks of congenital anomalies. (II-2A)

9. A careful history should be obtained to identify other factors, such as a positive family history or advanced maternal age, that may further increase the risk of congenital structural or chromosomal abnormalities. (II-2A)

10. Pregnancy in women with diabetes should be planned. Good contraceptive advice and pre-pregnancy counselling are essential. Euglycemia should be maintained before and during pregnancy. (II-2A)

11. All women with diabetes should be counselled regarding intake of foods high in folic acid, folate-fortified foods, and appropriate folic acid supplementation of 4 to 5 mg per day pre-conceptionally and in the first 12 weeks of gestation. (II-2A)

12. A substantial number of women with diabetes do not access pre-conception care programs. Strategies are needed to improve access to such programs and to maximize interventions associated with improved pregnancy outcomes, such as folic acid use. (II-2A)

Validation: These guidelines have been reviewed by the Genetics Committee and the Maternal Fetal Medicine Committee of the SOGC. Final approval has been given by the Executive and Council of the Society of Obstetricians and Gynaecologists of Canada.

Sponsors: The Society of Obstetricians and Gynaecologists of Canada

ABBREVIATIONS

β-HCG   beta-human chorionic gonadotropin

BMI   Body mass index

GU   genitourinary

HbA1c   hemoglobin A1c

PAPP-A pregnancy-associated plasma protein A

INTRODUCTION

Approximately 2% to 3% of babies born in Canada each year have major congenital anomalies, which are known to be associated with significant perinatal and infant morbidity and mortality.[1] Although infant mortality due to congenital anomalies has decreased from 3.1 per 1000 live births in 1981 to 1.9 per 1000 live births in 1995, birth defects remain a leading cause of death among Canadian infants in the neonatal period and during infancy.[1] Most major structural malformations due to environmental exposure to teratogens occur during embryogenesis and organogenesis, between the third and seventh weeks of gestation.[2] Details of teratology are summarized in the SOGC Consensus document, "Principles of human teratology: drug, chemical, and infectious exposure."[3]

This guideline reviews the current data available on the risk of congenital anomalies in pregnancies complicated by pre-existing or gestational diabetes, according to the evaluation of evidence criteria of the Canadian Task Force on Preventive Health Care (Table 1).[4] The guideline does not address maternal or other fetal and neonatal complications associated with pre-existing and gestational diabetes. The Cochrane Library and Medline were searched for English-language articles published from 1990 to February 2005, relating to pre-existing and gestational diabetes and fetal abnormalities. Search terms included pregnancy, diabetes mellitus, pre-existing diabetes, pregestational diabetes, type 1 diabetes, type 2 diabetes, insulin dependent diabetes, gestational diabetes, impaired glucose tolerance, congenital anomalies, malformations, and stillbirth. Additional publications were identified from the bibliographies of these articles as well as the Science Citation Index. All study types were reviewed. Randomized controlled trials were considered evidence of the highest quality, followed by cohort studies. Key studies and supporting data for each recommendation are summarized with evaluative comments and referenced.

PATHOPHYSIOLOGY

Although the majority of congenital anomalies have unexplained causes, about 10% can be attributed to environmental factors such as maternal medical illness.[1] One of the best-studied maternal metabolic diseases associated with fetal malformation is diabetes mellitus. Diabetes is characterized by hyperglycemia and disturbances of carbohydrate, fat, and protein metabolism associated with absolute or relative deficiencies in insulin secretion and/or insulin action.[5] Diabetic embryopathy, a spectrum of congenital malformations or disruptions considered to be caused by maternal diabetes mellitus, is a diagnosis of exclusion.[6]

The pathogenesis of fetal malformations associated with pre-existing diabetes is poorly understood but may be multifactorial and related to nutrient deficiencies or toxic metabolites. Hyperglycemia, hypoxia, ketone and amino acid abnormalities, and glycosylation of proteins have been reported as potential teratogens that may alter molecular signalling pathways and adversely affect embryogenesis.[7] Information regarding the teratogenicity of diabetes has been obtained from animal models and human studies. Hypoglycemia in animal studies has been shown to interfere with normal cardiogenesis and alters morphology, function, metabolism, and expression of certain proteins in the developing heart.[8–11] Hyperglycemia, beta-hydroxybutyrate (the major ketone produced in ketoacidosis) and somatomedin inhibitors have been associated with neural tube defects.[7] Hyperglycemia may also precipitate the release of free radicals causing the disruption in signal transduction. Insulin, free fatty acids, and branched chain amino acids, which also accumulate in the serum of diabetics, are not toxic to embryos in culture.[7]

Recommendation

1. Experimental studies suggest that hyperglycemia is the major teratogen in diabetic pregnancies, but other diabetes-related factors may also affect fetal outcomes. Further research using animal models is required to clarify the teratogenic factors associated with pre-existing and gestational diabetes (II-3C).

STRUCTURAL CONGENITAL ABNORMALITIES

The risk of major malformations is markedly increased in infants of diabetic mothers, ranging from 4% to 10%, which is 2- to 3-fold higher than in the general population, with even higher absolute and relative risks for particular malformations, such as neural tube defects (1% risk).[12]

The most common anomalies associated with pre-existing diabetes involve the cardiovascular system, the central nervous system, and the face and extremities (Table 2). Specific abnormalities associated with diabetic pregnancies are cardiovascular (such as transposition of the great vessels, ventricular septal defect, situs inversus, single ventricle. and hypoplastic left ventricle), central nervous system (such as anencephaly, encephalocele, meningomyelocele, spina bifida, and holoprosencephaly), musculoskeletal (such as caudal regression), genitourinary (such as renal agenesis and multicystic dysplasia), and gastrointestinal (such as anal/rectal atresia and small left colon).[13,14] In the offspring of women with pre-existing diabetes, the incidence of cardiovascular abnormalities ranges from 2 to 34 per 1000 births, central nervous system abnormalities from 1 to 5 per 1000 births, musculoskeletal abnormalities from 2 to 20 per 1000 births, genitourinary abnormalities from 2 to

Table 2. Malformations associated with pre-existing diabetes

Central nervous system	Open neural tube defects, holoprosencephaly, absent corpus callosum, Arnold-Chiari anomaly, schizencephaly, microcephaly, macrocephaly, agenesis of olfactory tracts, hydrocephaly
Cardiovascular system	Transposition of the great vessels, ventricular septal defect, atrial septal defect, tetralogy of Fallot, coarctation, single umbilical artery, hypoplastic left ventricle, cardiomegaly
Gastrointestinal system	Pyloric stenosis, duodenal atresia, microcolon, anorectal atresia, omphalo-enteric cyst/fistula, hernias
Urogenital system	Renal agenesis, renal cysts, hydronephrosis, duplication of ureter, ureterocele, uterine agenesis, hypoplastic vagina, micropenis, hypospadias, cryptorchidism, hypoplastic testes, ambiguous genitalia
Musculoskeletal system	Caudal dysgenesis, craniosynostosis, costovertebral anomalies, limb reduction, club foot, contractures, polysyndactyly
Other	Cleft palate

32 per 1000 births, and gastrointestinal abnormalities from 1 to 5 per 1000 births.[13,15,16]

CHROMOSOMAL ABNORMALITIES

Studies addressing the risk of aneuploidy with diabetes suggest that chromosomal abnormalities occurring with pre-existing diabetes are likely associated with the risks of increasing maternal age.[16,17] However, the paucity of data that include second trimester pregnancy terminations for chromosomal abnormalities may bias these findings.

PRE-EXISTING DIABETES

The cause of type 1 diabetes is an absolute deficiency of insulin secretion.[5] The cause of type 2 diabetes is a combination of resistance to insulin action and an inadequate compensatory insulin secretory response.[5] Rates of fetal malformation appear to be similar for maternal type 1 and type 2 diabetes.[18] Adjusted results of population-based registry and database studies evaluating the risk of congenital anomalies (excluding terminations) show anomalies for pre-existing diabetes (type 1 or type 2) 1.9 to 10 times higher than in the total population.[13,15,16,19] Population-based prospective cohort studies that include second trimester terminations of pregnancy have demonstrated a 1.7- to 3-fold increase in risk of congenital abnormalities in women with type 1 diabetes compared with the background population. As there was a high frequency of planned pregnancies, overall good early glycemic control, and appropriate use of folic acid in these studies, this suggests that variability in glycemic control may be an important factor.[20,21]

Studies have presented contradictory evidence regarding the influence of cultural, racial, or ethnic differences in rates of malformations.[16,19,22,23] Studies examining glycemic control and birth defects have demonstrated a dose-response effect: the poorer the glucose control periconceptionally or in early pregnancy, the greater the risk for congenital anomalies.[24–29]

Recommendation

2. Prospective and retrospective cohort studies have demonstrated an increased risk of congenital abnormalities with pre-existing diabetes. Further studies that include outcomes from first and second trimester pregnancy terminations, account for potential confounding variables, and use appropriate control groups are required. (II-2A)

GESTATIONAL DIABETES

Gestational diabetes is a group of glucose intolerant conditions that has its onset or is first recognized during pregnancy and complicates 2% to 4% of all pregnancies.[30–32] Adjusted results of population-based registry and database studies evaluating the risk of congenital anomalies (excluding terminations) show anomalies for gestational diabetes 1.2 times higher than in the total population (95% CI 1.1–1.3).[16] Adjusted analyses of a population-based database study evaluating risk of congenital anomalies, excluding terminations, show a 3.4-fold increase in anomalies for women with gestational diabetes with fasting hyperglycemia ($P < 0.001$), and no difference in risk for women with gestational diabetes with normal fasting glucose compared with women without diabetes.[15]

Case series and cohort studies have demonstrated phenotypes in gestational diabetes consistent with those seen in the offspring of women with pre-existing diabetes.[27,33,34] Studies based on registry data (excluding second trimester terminations for congenital anomalies) suggest a small but statistically significant increase in holoprosencephaly, costovertebral, and GU tract anomalies in offspring of women with gestational diabetes compared with women without diabetes.[14] A population-based registry study demonstrated a total malformation rate in offspring of women with gestational diabetes similar to the general population (5.7%). However, among women with gestational diabetes, there was an increase in specific malformations in their offspring, typical of the embryopathy seen in type 1 diabetes, suggesting that a subgroup of women with gestational

diabetes may have undetected type 2 diabetes.[13] In women with gestational diabetes, increasing hyperglycemia at diagnosis was associated with an increasing risk of anomalies.[27] One prospective study demonstrated that women with gestational diabetes overall had a risk for congenital anomalies similar to that in the general population. However, in women with diabetes on early postpartum testing, who were likely to have had unrecognized type 2 diabetes, the rate of major congenital anomalies (4.6%) was the same as for women with established type 1 (5.9%) or type 2 (4.4%) diabetes.[30] Women at high risk for gestational diabetes may benefit from early glucose screening.[35]

Recommendations

3. Prospective and retrospective cohort studies have demonstrated an increased risk of congenital abnormalities with gestational diabetes. This observation is probably related to the inclusion of women with unrecognized type 2 diabetes. Clarification of the relationship between gestational diabetes and congenital abnormalities by studies that include outcomes from first and second trimester pregnancy terminations, account for potential confounding variables, and use appropriate control groups are required. (II-2A)

4. In some women, type 2 diabetes may be identified for the first time in pregnancy. Pre-conception recognition of women at high risk for type 2 diabetes and optimal glycemic control may reduce the risk of congenital anomalies. (II-2A)

MEDICATIONS

Maternal insulin does not cross the placenta and does not reach the embryo during organogenesis, so exogenous insulin is likely not the cause of congenital abnormalities associated with diabetes. The risk of congenital anomalies in fetuses of women with gestational diabetes has been reported to be increased if insulin therapy is required, and this population likely includes women with severe hyperglycemia and unrecognized type 2 diabetes whose fetuses have been exposed to first trimester hyperglycemia before or during organogenesis.[36]

Animal and human studies assessing the teratogenic effects of oral antihyperglycemic agents have yielded conflicting data because the risk of major malformations in infants of diabetic mothers appears to be related to maternal glycemic control rather than the antidiabetic therapy.[18] Sulfonylureas are used to treat hyperglycemia by stimulating insulin release from pancreatic beta cells. First generation sulfonylureas (such as chlorpropamide) have been shown to cross the placenta; however, the newer second-generation sulfonylureas (such as glyburide) may not cross the placenta, and less fetal exposure may occur. Less is known

about the teratogenic risk associated with the treatment of diabetes mellitus with biguanides (such as glucophage, which increase insulin action in peripheral tissues and reduce hepatic glucose output through inhibition of gluconeogenesis). Biguanides cross the placenta, and, although they do not appear teratogenic, they have been associated with other adverse perinatal outcomes such as gestational hypertension and increased perinatal mortality when used for treatment in diabetic pregnancies.[37] There is limited information on other oral antihyperglycemics such as meglitinides, alpha-glucosidase inhibitors, and thiazolidinediones, and therefore their use in pregnancy cannot be recommended.

Although there is evidence from animal studies that suggest that insulin glargine is safe and efficacious in pregnancy,[38] only case reports and small case series attest to the safety in human pregnancies.[39–41]

Recommendation

5. Second generation sulfonylureas have not been associated with congenital abnormalities in human studies. The use of biguanides may be associated with other adverse perinatal outcomes. The use of other oral antihyperglycemic agents is not recommended in pregnancy. (II-2A)

EFFECT OF OBESITY

Obesity is a well-known risk factor for diabetes,[42] and its association with congenital anomalies has been established in many studies.[43–45] Obesity and diabetes may have metabolic abnormalities in common, including insulin resistance and hyperinsulinemia.[46] Studies in women with pre-existing diabetes (type 1 or type 2) and a pre-pregnancy BMI = 28 kg/m^2 have shown a 3-fold increase (adjusted rates) in the risk of congenital abnormalities (excluding second trimester terminations of pregnancy).[47] Studies evaluating the risk for congenital anomalies show that there is a multiplicative 3-fold increase (adjusted rates) in risk when the combined effects of maternal obesity (pre-pregnancy BMI = 30.0 kg/m^2) and gestational diabetes are considered, and that the risk increases with increasing BMI.[46,48]

Recommendation

6. The risk of congenital abnormalities is increased in the offspring of obese women with diabetes. A healthy diet and regular exercise may help optimize pre-pregnancy weight and reduce the risk of congenital anomalies. (II-2A)

PRENATAL DIAGNOSIS

SOGC recommends that prenatal screening for chromosomal and structural defects be available to all pregnant women. Although the risk of fetal chromosomal

abnormality is not generally considered to be increased in women with diabetes,[17] median levels of alpha-fetoprotein and unconjugated estriol are typically lower in women with pre-existing diabetes, and maternal serum screening programs adjust the marker levels to take account of this difference.[49] A first trimester ultrasound examination for dating purposes may be useful for monitoring fetal growth later in pregnancy even when aneuploidy screening is not appropriate or desired. Ultrasound examination for fetal morphology, including a detailed assessment of cardiac anatomy, should be offered at 18 to 20 weeks. In selected cases, repeat morphology scanning with echocardiography may help to better define cardiac structures.

Recommendation

7. Accurate determination of gestational age is required in women with diabetes. Given the increased risk of congenital abnormalities, they should be offered appropriate biochemical and ultrasonographic screening and a detailed evaluation of fetal cardiac structures. (II-2A)

PRE-CONCEPTION COUNSELLING

Because the types of defects induced by maternal diabetes have their origins at early stages of embryogenesis, it is important to introduce prevention strategies before conception. The majority of women do not seek their first prenatal visit until after the time of embryogenesis, and unplanned pregnancies occur in about one half to two thirds of women with diabetes.[50,51] Women who do not present for pre-conception care are more likely to be young, less likely to be married, more likely to smoke, and to be low socioeconomic status.[52] With pre-existing diabetes, prospective studies and meta-analyses have demonstrated that pre- conception counselling with optimization of glycemic control before conception with a multidisciplinary team can significantly lower the prevalence of major congenital anomalies.[21,23,47,52–58] Studies emphasize the benefits of providing optimal pre-conception and early pregnancy care with centralization and early referral for care with a multidisciplinary team for pregnant women with diabetes to reduce the risks of congenital anomalies.[21,55,59] Pre-conception measurements of glycosylated hemoglobin or first trimester glucose and glycosylated hemoglobin may be used to counsel women with pre-existing diabetes about the risk of congenital abnormalities, and measurements of glycosylated hemoglobin may be used to counsel women with gestational diabetes.[60] Achieving and maintaining euglycemia is the main goal of management for pregnancies complicated by pre-existing or gestational diabetes to reduce the risk of congenital abnormalities. The Canadian Diabetes Association recommends that pregnant women with type 1 or type 2 diabetes should strive to attain a pre-conception glycosylated hemoglobin (HbA1c) $\leq$ 7% to decrease the risk of congenital malformations.[12] In addition, folic acid supplementation of 1 to 5 mg per day beginning before conception and continuing until 13 weeks' gestation is recommended by the Canadian Diabetes association[12] and the Society of Obstetricians and Gynaecologists of Canada.[61]

Recommendations

8. Women with diabetes should be offered pre-conception counselling with a multidisciplinary team to optimize general health and glycemic control and to review the risks of congenital anomalies. (II-2A)

9. A careful history should be obtained to identify other factors, such as a positive family history or advanced maternal age, that may further increase the risk of congenital structural or chromosomal abnormalities. (II-2A)

10. Pregnancy in women with diabetes should be planned. Good contraceptive advice and pre-pregnancy counselling are essential. Euglycaemia should be maintained before and during pregnancy (II-2A).

11. All women with diabetes should be counselled regarding intake of foods high in folic acid, folate-fortified foods and appropriate folic acid supplementation of 4 to 5 mg per day pre-conceptionally and in the first 12 weeks of gestation. (II-2A)

12. A substantial number of women with diabetes do not access pre-conception care programs. Strategies are needed to improve access to such programs and to maximize interventions associated with improved pregnancy outcomes, such as folic acid use. (II-2A)

LIMITATIONS OF STUDIES

A number of methodological issues affect the evaluation of the relationship between congenital anomalies and pre-existing and gestational diabetes. A review of the evidence demonstrates limitations in these studies such as retrospective, non-standardized data collection, grouping of type 1 and type 2 diabetes populations, non-standardized classification of type of diabetes, glycemic control, and congenital malformations, a paucity of information on potential confounding factors (such as maternal age, level of glucose control, use of folic acid, and use of oral antihyperglycemic agents), lack of outcome data on first and second trimester pregnancy terminations for prenatally diagnosed congenital anomalies, inclusion of anomalies due to other causes, and small sample sizes. Control groups may have included women with undiagnosed diabetes. Biases include publication, reporting, selection, and ascertainment. Although a recent well-designed meta-analysis evaluated the effect of diabetes on the rate of congenital anomalies and the effect

of pre-conception counselling on the rate of congenital anomalies,[54] structured, prospective, and comprehensive data collection remains important for evaluation of the association of pre-existing and gestational diabetes with congenital abnormalities.

SUMMARY

The majority of pregnancies complicated by pre-existing and gestational diabetes are not associated with congenital abnormalities and result in the birth of healthy newborns. However, the evidence consistently confirms that pregnancies complicated by diabetes are associated with an increased risk of congenital malformations that varies with the degree of pre-conception glycemic control and other mitigating factors such as folic acid supplementation.

Further research is required with animal models to clarify the factors affecting the teratogenic potential of diabetes. Further research with well-constructed, prospective, nationally regulated data collection accounting for important confounding variables and minimizing bias is needed to help verify the associations between pre-existing and gestational diabetes and congenital abnormalities. Current studies highlight the importance of prospective population-based studies that clearly describe the criteria used for diagnosing diabetes and congenital abnormalities and that include second trimester termination of pregnancy. An optimal outcome may be obtained if good diabetic control is achieved before and during pregnancy. This requires careful planning of the pregnancy, early antenatal care, frequent obstetric and diabetic surveillance, and access to neonatal supportive care.

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