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FROM THE FAMILY PRACTICE INQUIRIES NETWORK

Does tight control of blood glucose in pregnant women with diabetes improve neonatal outcomes?

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EVIDENCE-BASED ANSWER

In pregnant women with preexisting type 1 diabetes mellitus, maintaining near-normal blood glucose levels decreases the rate of major congenital anomalies (defined as those causing death or a serious handicap necessitating surgical correction or medical treatment). Prolonged preconception control of blood sugar to near normal levels reduces the rate of major congenital anomalies close to those seen in women without diabetes (strength of recommendation [SOR]: **A**, based on prospective cohort studies and randomized controlled trial [RCT]).

Intensive management reduces the risk of congenital anomalies more than conventional therapy, and lowers the risk of neonatal hypoglycemia (SOR: **B**, based on RCT). Very tight control does not reduce clinically significant neonatal morbidity but does increase the risk of maternal hypoglycemia (SOR: **B**, based on a systematic review). Evidence is insufficient about whether or not these statements hold true for women with type 2 diabetes.

In women with impaired glucose tolerance, dietary control reduces neonatal hypoglycemia. To date, studies have not found statistically significant reductions in admission rates to the special care nursery or birth weights above the 90th percentile (SOR: **B**, systematic review). Evidence is insufficient to suggest improved outcomes with therapy in women with gestational diabetes. Standard recommendations typically recommend tight control in this population as well.

EVIDENCE SUMMARY

Two studies show that in type 1 diabetes mellitus, elevated blood glucose levels in early pregnancy (HbA_{1c}=6%–8%) are associated with a threefold increase in fetal malformations.[1,2] Maintaining preconception and early pregnancy blood glucose levels in the normal range can reduce this risk. A meta-analysis comparing 16 studies of women with pregestational diabetes—13 of which included only women with type 1 diabetes—

found that women receiving preconception care had lower early first trimester HbA_{1c} levels than those who did not (7.9% vs 9.6%) and delivered fewer infants with major congenital anomalies (relative risk [RR]=0.36; 95% confidence interval [CI], 0.22–0.59).[2] One limitation of this study was that preconception care was not consistently defined among the included studies.

A 10-year RCT evaluated the outcomes of 270 pregnancies in women who had received either intensive (SQ infusion or multiple daily injections) or conventional insulin regimens prior to pregnancy. Women were advised to use intensive therapy when they were trying to conceive, and all were changed to intensive therapy if pregnancy was confirmed. Women in the intensive therapy group had normal HbA_{1c} levels for an average of 40 months before conception. Women receiving intensive therapy had lower mean HbA_{1c} levels at conception (7.4 ± 1.3 SD vs 8.1 ± 1.7 SD) and fewer major congenital anomalies (0.7% vs 5.9%; number needed to treat=19) than did women in the conventional group. When infants with genetic malformations were excluded from the analysis, rates of congenital malformations were similar in women switched to intensive therapy either before or after conception (3.8% vs 3.6%). No differences were seen between neonatal mortality, spontaneous abortion rates, birth weights, Apgar scores, and hypocalcemia or hypoglycemia rates.[3]

When tight and very tight control of glucose in pregnant women with pregestational diabetes were compared in a Cochrane systematic review, rates of maternal hypoglycemia in the very tightly controlled group were higher (odds ratio [OR]=25.96; 95% CI, 4.91–137.26).[5] An RCT of 118 women with pregestational diabetes compared 4-times-daily vs twice-daily doses of insulin. Infants born to women receiving 4-times-daily insulin had significantly lower rates of neonatal hypoglycemia (RR=0.17; 95% CI, 0.04–0.74). While the trend was toward improved neonatal metabolic effects in the trials, the clinical significance of these findings is not clear.

Whether or not treatment of gestational diabetes improves outcomes is uncertain. A Cochrane systematic review evaluating a small number of trials, with variable quality and inconsistent outcome measures, compared dietary management to routine care in gestational diabetics. While fewer infants with birth weights >4000 g were delivered in the diet therapy group (OR=0.78; 95% CI, 0.45–1.35), the results were not statistically significant. No other important clinical differences were found.[6]

Another Cochrane systematic review evaluated the effects of dietary treatment of women with impaired glucose tolerance and gestational diabetes. Three trials with a total of 223 women with impaired glucose tolerance found a significant reduction in the rate of neonatal hypoglycemia (RR=0.25; 95% CI, 0.07–0.86). There was no significant change in the rates of cesarean section (RR=0.86; 95% CI, 0.51–1.45), admission to the special care nursery (RR=0.49; 95% CI, 0.19–1.24), or birth weights greater than the 90th percentile (RR=0.55; 95% CI, 0.19–1.61). Inadequate power may well account for the failure to reach significance in these outcomes.[7]

RECOMMENDATIONS FROM OTHERS

The American College of Obstetrics and Gynecology (ACOG) recommends that women with pregestational diabetes maintain fasting plasma glucose levels between 60–90 mg/dL and 2-hour postprandial levels <120 mg/dL.[8] For women with gestational diabetes who are not controlled within these targets on dietary therapy alone, ACOG recommends the additional of insulin therapy.[9]

The American Diabetes Association recommends that women with pregestational diabetes maintain capillary plasma glucose levels of 80–110 mg/dL before and <155 mg/dL 2 hours after meals before pregnancy and while trying to conceive.[10] The ADA does not list target glucose levels for women with pregestational diabetes once they become pregnant. The ADA recommends the use of diet and insulin therapy to maintain preprandial plasma glucose levels of <105 mg/dL and 2-hour postprandial levels below <130 mg/dL in gestational diabetes.[11]

CLINICAL COMMENTARY

Glucose control makes a difference for pregnancy outcomes in type I diabetes

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It is well accepted that glucose control makes a difference for pregnancy outcomes in women with type 1 diabetes. Since similar studies have not been done in women with preexisting type 2 diabetes, we have to assume that the risk is also high for them. Preconception counseling about glucose control is so important for women with diabetes. Fortunately, because they generally have routine visits for their chronic care, we have an opportunity to initiate discussion of glucose control in relationship to pregnancy planning. Routine diabetes care visits also give us the opportunity to discuss other important preconception topics.

REFERENCES

1. Vaarasmaki MS, Hartikainen A, Anttila M, Pramila S, Koivisto M. Factors predicting peri- and neonatal outcome in diabetic pregnancy. *Early Hum Dev* 2000;59:61–70.
2. Ray JG, O'Brien TE, Chan WS. Preconception care and the risk of congenital anomalies in the offspring of women with diabetes mellitus: a meta-analysis. *QJM* 2001;94:435–444.
3. Pregnancy outcomes in the Diabetes Control and Complications Trial. *Am J Obstet Gynecol* 1996;174:1343–1353.
4. Nachum Z, Ben-Shlomo I, Weiner E, Shalev E. Twice daily versus four times daily insulin dose regimens for diabetes in pregnancy. *BMJ* 1999;319:1223–1227.
5. Walkinshaw SA. Very tight versus tight control for diabetes in pregnancy (Cochrane Review). In: *The Cochrane Library*, Issue 4, 2003. Chichester, UK: John Wiley & Sons, Ltd. Last updated 2-15-1999. Accessed on January 4, 2004.
6. Walkinshaw SA. Dietary regulation for 'gestational diabetes' (Cochrane Review). In: *The Cochrane Library*, Issue 4, 2003. Chichester, UK: John Wiley & Sons, Ltd.

Last updated 2-25-1999. Accessed on January 4, 2004.

7. West J, Walkinshaw SA. Treatments for gestational diabetes and impaired glucose tolerance in pregnancy (Cochrane Review). In: *The Cochrane Library*, Issue 4, 2003. Chichester, UK: John Wiley & Sons, Ltd. Last updated 9-12-2002. Accessed on January 4, 2004.
8. ACOG technical bulletin Diabetes and pregnancy. Number 200—December 1994 (replaces No. 92, May 1986). Committee on Technical Bulletins of the American College of Obstetricians and Gynecologists. *Int J Gynaecol Obstet* 1995;48:331–339.
9. Gestational Diabetes. ACOG Pract Bull No. 30. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2001;98:525–538.
10. Preconception care of women with diabetes. *Diabetes Care* 2004;27 Suppl 1:S76–S78. Available at: **care.diabetesjournals.org/cgi/content/full/27/suppl_1/s76**. Accessed on January 4, 2004.
11. Gestational diabetes mellitus. *Diabetes Care* 2003;26 Suppl 1:S103–S105. Available at: **care.diabetesjournals.org/cgi/content/full/26/suppl_1/s103**. Accessed on January 4, 2004.

DRUG BRAND NAMES

Allopurinol • Lopurin, Zyloprim
Amitriptyline • Elavil, Endep
Benzbromarone • Urinorm
Botulinim toxin A • Botox
Clindamycin • Cleocin
Fluoxetine • Prozac
Fluticasone • Flovent
Gabapentin • Neurontin
Metronidazole (intravaginal) • MetroGel
Probenecid • Benemid, Probalan
Sumatriptan • Imitrex
Tizanidine • Zanaflex
Triamcinolone • Azmacort
Valproate • Depacon