Title: Urine-based Ketone Testing in Pregnancy Complicated by Diabetes

Date: 20 July 2007

Context and policy issues:

Approximately 2% to 5% of all pregnancies are complicated by diabetes mellitus,\textsuperscript{1,2} an estimated 10% to 35% of which are due to pre-existing type 1 or type 2 diabetes mellitus, termed pregestational diabetes mellitus (PDM).\textsuperscript{1-3} The remaining 65% to 90% of cases are due to gestational diabetes mellitus (GDM),\textsuperscript{1-3} defined as glucose intolerance that initially occurs or is first recognized during pregnancy.\textsuperscript{4} A disproportionate number of Canada's GDM cases occur in the aboriginal population, with GDM affecting 8.0% to 18.0% of pregnancies, compared to 3.5% to 3.8% of pregnancies in the non-aboriginal population.\textsuperscript{4}

Both PDM and GDM are associated with numerous maternal and fetal complications, two of which include maternal diabetic ketoacidosis (DKA) and starvation ketosis.\textsuperscript{1,3} A number of metabolic changes occur with pregnancy, the purpose of which are to supply energy to the fetus. Levels of counter-regulatory hormones (e.g. cortisol) increase, creating a state of relative insulin resistance.\textsuperscript{5} As well, lipolysis is enhanced, levels of free fatty acids increase, and ketogenesis may occur.\textsuperscript{5} Ketosis is relatively common in pregnancy with about 30% of all pregnant women having detectable amounts of ketones in their first morning urine.\textsuperscript{6}

DKA can occur in individuals with PDM (generally those with pre-existing type 1 diabetes) when exogenous insulin requirements increase with advancing gestation, but insulin dosage adjustments do not keep pace.\textsuperscript{5} This insulin deficiency prevents glucose utilization at the cellular level, leading to the release of counter-regulatory hormones that facilitate the use of alternate energy sources including adipose tissue.\textsuperscript{5} Fats are then broken down in large quantities and oxidized in the liver to ketone bodies, which accumulate in the blood and pass into the urine.\textsuperscript{5} DKA is a potentially life threatening condition because it lowers blood pH, affecting the function of a number of metabolic enzymes. Further, hyperglycemia associated with DKA leads to dehydration, hypovolemia, electrolyte abnormalities, and hyperosmolar. Multiple organ

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systems can be affected, leading to shock, coma and even death. Fortunately, maternal death is relatively rare, but fetal mortality occurs in about 10% of cases. For those who survive, ketosis can have significant adverse effects on the baby’s brain development and can affect future intellectual and learning capacity.

Starvation ketosis can occur in individuals with PDM or GDM when caloric intake is insufficient. The body’s glucose supply becomes depleted and fat is used as an alternate energy source. As with DKA, the broken down fats are oxidized in the liver to ketone bodies, which accumulate in the blood and pass into the urine. Starvation ketosis can be distinguished from DKA in that blood glucose tends to be low or only slightly elevated, whereas DKA is characterized by hyperglycemia. GDM is primarily managed with medical nutritional therapy, but caloric intake must remain sufficient to avoid starvation ketosis and its sequelae.

To monitor for DKA and starvation ketosis during pregnancy, ketones can be detected in the urine using a dipstick test, or measured in the blood through home-based and lab testing. Generally, urine-based tests detect ketones via a colorimetric reaction between acetoacetate and a nitroprusside reagent, although some tests may also detect acetone. The most common blood-based tests for ketones usually quantify β-hydroxybutyrate, the predominant ketone body, via an enzymatic method.

**Research questions:**

1. What is the clinical and cost effectiveness of urine ketone testing in pregnant women with pre-existing diabetes and in gestational diabetes?

2. What are the current guidelines for urine ketone testing in pregnant women with pre-existing diabetes and in gestational diabetes?

**Methods:**

A literature search was conducted on key health technology assessment resources, including PubMed, Embase in OVID, The Cochrane Library (Issue 2, 2007), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI’s HTAIS, EuroScan, international HTA agencies, and a focused Internet search. Results include English language publications from 2002 to date. Links to online full-text are provided when available.

**Summary of findings:**

1. **What is the clinical and cost effectiveness of urine ketone testing in pregnant women with pre-existing diabetes and in gestational diabetes?**

The literature search did not identify any health technology assessments, meta-analyses or controlled studies of the clinical effectiveness of urine ketone testing in PDM or GDM. Further, the literature search did not identify any economic evaluations of urine ketone testing in PDM and GDM.

The American Diabetes Association’s position statement on tests of glycemia does, however, state that urine ketone testing is not considered reliable for diagnosing and monitoring of ketoacidosis. Since urine-based testing detects acetoacetate rather than β-hydroxybutyrate, it may underestimate the total ketone body concentration. Further, urine-based testing can produce false positive results with highly coloured urine or in the presence of drugs that contain
sulfhydryl groups, such as captopril.\(^6\) False negative results may be produced with highly acidic urine and when test strips are exposed to air for extended periods of time.\(^6\) Finally, urine-based testing for ketones may not provide timely information if the urine that is tested has sat in bladder for a significant duration of time prior to testing.\(^9\)

2. What are the current guidelines for urine ketone testing in pregnant women with pre-existing diabetes and in gestational diabetes?

**Pregestational Diabetes Mellitus**

A number of diabetes management guidelines or position statements include general recommendations for ketone testing in PDM.\(^6,12-14\) While the practice of ketone testing is recommended during pregnancy, guidelines tend to be vague with respect to either the method (i.e., urine or blood), frequency or timing of testing,\(^6,12,13\) with the exception of the British Columbia Reproductive Care guidelines\(^14\) (Table 1). These guidelines specify twice daily urine ketone testing in individuals with type 1 or type 2 PDM as outlined in Table 1.

### Table 1: Recommendations for urine-based ketone monitoring in pregestational diabetes mellitus

<table>
<thead>
<tr>
<th>Practice Guideline or Position Statement</th>
<th>Organization, Year of Publication</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-existing Diabetes and Pregnancy(^13)</td>
<td>Canadian Diabetes Association, 2003</td>
<td>'Since starvation ketosis is common in pregnancy and may have detrimental effects on the fetus, urine and/or blood monitoring of ketones is warranted to confirm that the diet is adequate.'</td>
</tr>
<tr>
<td></td>
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<td>'Ketosis should be avoided during pregnancy [Grade C, Level 3].'</td>
</tr>
<tr>
<td>Obstetric Guideline 10B: Diabetes Mellitus and Pregnancy Type 1 &amp; 2(^14)</td>
<td>British Columbia Reproductive Care Program, 2001</td>
<td>Urine ketone testing is recommended daily before breakfast and supper, if glucose values are high, and when sick. If ketonuria is detected, it is recommended that all voiding is tested until the urine is clear of ketones.</td>
</tr>
<tr>
<td>Tests of Glycemia(^6)</td>
<td>American Diabetes Association, 2003</td>
<td>'Ketone testing is an important part of monitoring in type 1 diabetic patients, in pregnancy with pre-existing diabetes, and in gestational diabetes.'</td>
</tr>
<tr>
<td></td>
<td></td>
<td>'Patients with type 1 diabetes should test for ketones during acute illness or stress or when blood glucose levels are consistently elevated (e.g., &gt;300 mg/dl [&gt;16.7 mmol/l]), during pregnancy, or when any symptoms of ketoacidosis, such as nausea, vomiting, or abdominal pain, are present.'</td>
</tr>
<tr>
<td>Section 8; Pregnancy and Diabetes(^12)</td>
<td>Indiana State Health Department, 2004</td>
<td>'Urine ketone testing is recommended daily during pregnancy, in addition to blood glucose monitoring.'</td>
</tr>
</tbody>
</table>
Gestational Diabetes Mellitus

A number of practice guidelines for GDM recommend urine or blood-based monitoring of ketones to ensure that the maternal diet is sufficient to prevent starvation ketosis (Table 2). Generally, urine-based testing for ketones is recommended, but the Canadian Diabetes Association guidelines state that urine and/or blood-based testing can be used. The British Columbia Reproductive Care Program guidelines, South Dakota Gestational Diabetes Care Guidelines, and the Wyoming Clinical Practice Recommendations for Diabetes Mellitus provide more detail with respect to timing, frequency and duration of testing.

Table 2: Recommendations for urine-based ketone monitoring in gestational diabetes mellitus

<table>
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<tr>
<td>Gestational Diabetes Mellitus&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Canadian Diabetes Association, 2003</td>
<td>'Since starvation ketosis is common in pregnancy and may have detrimental effects on the fetus, urine and/or blood monitoring of ketones is warranted to confirm that the diet is adequate.'</td>
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<tr>
<td>Obstetric Guideline 10A: Gestational Diabetes&lt;sup&gt;15&lt;/sup&gt;</td>
<td>British Columbia Reproductive Care Program, 2001</td>
<td>Daily urine ketone testing is recommended before breakfast and supper.</td>
</tr>
<tr>
<td>Recommendations for Nutrition Best Practice in the Management of Gestational Diabetes Mellitus&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Canadian Diabetes Association, Dietitians of Canada, Diabete Quebec, and the Ordre Professionnel de dietetistes du Quebec, 2006</td>
<td>'Ketones should be monitored to verify that adequate calories are provided to prevent ketone formation, as recommended in the CDA Clinical Practice Guidelines.'</td>
</tr>
<tr>
<td>Gestational Diabetes Mellitus&lt;sup&gt;18&lt;/sup&gt;</td>
<td>American Diabetes Association, 2004</td>
<td>'Urine ketone monitoring may be useful in detecting insufficient calorie or carbohydrate intake in women treated with calorie restriction.'</td>
</tr>
</tbody>
</table>
| South Dakota Gestational Diabetes Care Guidelines<sup>16</sup> | South Dakota Department of Health, 2003 | 'Consider urine ketone testing if: ▪ Patient is obese (≥ 26 BMI) ▪ Patient experiences weight loss ▪ Insulin is initiated ▪ Patient has other illnesses

Discontinue ketone testing if all results are trace or less.

If results are frequently positive then a referral to an RD† for MNT‡ should be considered even if increased calories require initiation of insulin to achieve euglycemia.' |
| Section 8: pregnancy and diabetes.<sup>12</sup> | Indiana State Health Department, 2004 | 'Urine ketone testing during pregnancy is recommended, in addition to blood glucose monitoring.' |
Wyoming Clinical Practice Recommendations For Diabetes Mellitus

The Wyoming Diabetes Prevention and Control Program.

It is recommended that the first morning urine is tested for ketones. If urine ketones are positive, urine should be checked again later in day. If the urine tests positive for ketones then carbohydrate may need to be increased.

* Urine ketone monitoring is not recommended by the American Diabetes Association for diagnosing or monitoring of ketoacidosis†
† RD=Registered Dietician
‡ MNT=Medical Nutritional Therapy

Conclusions and implications for decision or policy making:

In summary, diabetic ketoacidosis and starvation ketosis can have serious consequences for both the mother and unborn child. Urine-based ketone testing can be used to detect established or impending ketoacidosis, but is not recommended for diagnostic or monitoring purposes. A search of the recent literature failed to locate information regarding the clinical and cost-effectiveness of urine ketone testing in PDM or GDM. Despite the lack of evidence, a number of clinical practice guidelines for PDM and GDM recommend the practice of urine and, in some cases, blood-based testing for ketones. Thus, these recommendations appeared to be based upon the potential for serious harm to the mother and baby should diabetic ketoacidosis or starvation ketosis develop.

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