Obstetric Medicine
Obstetric Medicine
2018, Vol. 11(2) 79–82

DOI: 10.1177/1753495X17743163
journals.sagepub.com/home/obm
SAGE

Prevalence of maternal urinary ketones in pregnancy in overweight and obese women

Helen L Robinson[1,2,3], Helen L Barrett[1,2,4], Katie Foxcroft[2], Leonie K Callaway[1,2,3,4] and Marloes Dekker Nitert[1,5]

Abstract

Background: Ketonuria may be associated with adverse fetal outcomes. This study aimed to determine the prevalence of ketonuria at three time points in pregnancy and to assess whether ketonuria correlates with a clinical indication for performing a urine test.

Methods: Women had fasting urinary ketone levels measured at 16 and 28 weeks gestation and random ketone levels measured close to 36 weeks gestation. All ketone levels in the third trimester were recorded along with the clinical indication for the test.

Results: One hundred and eighty-seven women were included in the study. Twenty-two per cent of women had ketonuria at either 16 or 28 weeks gestation and 8% at 36 weeks gestation. Ketonuria was significantly more likely if a test was performed for a clinical indication ($p = 0.0002$).

Conclusion: Ketonuria in pregnancy is common affecting at least one in five women. Ketonuria is more common in women who have a clinical indication for performing a urine test.

Keywords

Endocrinology, diabetes, metabolism, nutrition

Date received: 11 July 2017; accepted: 7 October 2017

Introduction

Ketonuria has been associated with adverse pregnancy outcomes in some but not all studies.[1,2] These outcomes include reduced childhood intelligence quota (IQ), oligohydramnios, fetal heart rate decelerations and non-reactive non-stress tests. The level of urinary maternal ketones that has been associated with these adverse pregnancy outcomes has been as low as 1–3 mmol/L, which equates to a trace to small level on a urine dipstick.[1]

Ketones, which consist of a mixture of acetoacetate, acetone and beta-hydroxybutyrate are produced from the breakdown of lipids when the body's metabolic needs are not met by glucose. Any reduction in glucose supply, such as from decreased oral intake or a diet low in carbohydrate, will result in an increase in ketone levels. Maternal ketones are supplied to the fetus through passive diffusion across the placenta.[3] In pregnancy, the synthesis of ketones is accelerated, particularly in the third trimester, due to high-energy demands and increased maternal lipid metabolism in response to increased maternal insulin resistance.[4,5]

The prevalence of ketonuria in pregnancy is not well characterized. Studies report a wide variation in prevalence ranging from 5% to 89% of women.[6,7] This discrepancy in prevalence is difficult to explain but may be due to heterogeneity in study design and patient population. Understanding the prevalence and clinical relevance of ketonuria in pregnancy is important. As the prevalence of obesity, pre gestational diabetes and gestational diabetes (GDM) has increased, dietary management approaches in pregnancy and their ketonuric consequences are important questions. Women regularly seek dietary advice during pregnancy, and low carbohydrate diets, which by definition are associated with ketonuria, have become increasingly popular. In routine management of hyperemesis, or intercurrent illness during pregnancy, the prevalence and long-term consequences of ketonuria has not been well understood.

A fundamental principle of clinical epidemiology is that association does not equal causation. While ketones have been associated with adverse pregnancy outcomes, there is no clear evidence that maternal ketones directly cause adverse pregnancy outcomes. Ketonuria may instead be a marker of maternal pathology that causes both an adverse fetal environment and elevated urinary ketone levels. Any pathology resulting in a decrease in glucose availability will lead to an increase in ketone levels. Likewise any pathology that leads to maternal dehydration will have the effect of increasing urinary ketone levels, secondary to a decrease in urinary volume. To our knowledge no previous studies have evaluated whether maternal ketonuria is more likely if a woman is acutely unwell or has a temporary change in her physiological status.

The purpose of this study was firstly to assess the prevalence of ketonuria in pregnancy, with a particular focus on whether prevalence changes with gestation. The second aim was to assess whether the presence of ketonuria correlates with a clinical indication for performing a urine test, such as maternal illness.

Methods

Women enrolled in the Study of PRobiotics IN Gestational diabetes (SPRING),[8] a study of probiotics to prevent GDM in overweight and obese women, provided fasting urine samples at a 16-week and 28-week gestation visit (ANZCTR 12611001208998). Women were asked to fast for 9.5 to 12 h. Water intake was encouraged during this fast to prevent dehydration. The presence of ketonuria was measured via urine dipstick testing for all patients enrolled at the Royal Brisbane and Women's Hospital site. Urine dipstick tests were

[1]UQ Centre for Clinical Research, The University of Queensland, Brisbane, Australia
[2]Obstetric Medicine, Royal Brisbane and Women's Hospital, Brisbane, Australia
[3]Department of Medicine, Ipswich Hospital, Ipswich, Australia
[4]Faculty of Medicine, The University of Queensland, Brisbane, Australia
[5]School of Chemistry and Molecular Biosciences, Faculty of Science, The University of Queensland, Brisbane, Australia

Corresponding author:
Helen L Robinson, UQ Centre for Clinical Research, The University of Queensland Building 71/918, RBWH Herston, Brisbane City, Queensland 4029, Australia.
Email: h.robinson@uq.edu.au

performed using SIEMENS Multistix 10 SG reagent strips, which measure urinary levels of acetoacetate. For this specific brand of reagent strips a ketone level of trace, small, moderate and large corresponded to an acetoacetate level of 0.5, 1.5, 4 and ≥ 8 mmol/L, respectively. For the purposes of this study, ketonuria is defined as present if there was a trace or more on the urine dipstick.

The rate of ketonuria in the late third trimester of the women in the SPRING study was determined by reviewing hospital charts for urine tests performed at routine clinic visits. The urine test performed at the clinic visit closest to 36 weeks gestation was included in the analysis of prevalence of urinary ketones. The urine ketone test may or may not have been performed in the fasting state. For the analysis of whether urinary ketones correlate with a clinical indication for performing a urine test, hospital charts were reviewed for all urinary ketone levels performed in the third trimester. For women with multiple urinary ketone tests performed during the third trimester, each result was recorded along with the reason for undertaking each test.

Data was analysed using the statistical program R, version 3.1.2. Chi-square statistics were used to evaluate whether ketonuria was more likely to be present in women undergoing urine tests for a clinical indication. Fisher's exact tests were used, when expected frequencies were low, to assess the relationship between ketonuria and patient demographics. $p < 0.05$ was considered statistically significant.

Ethical approval was granted from the Royal Brisbane and Women's Hospital Human Research Ethics Committee, HREC/11/QRBW/467. All women gave written informed consent prior to enrolment in the SPRING study.

Results

One hundred and ninety-five women were enrolled in the SPRING study at the Royal Brisbane and Women's Hospital site. Eight women withdrew from the study prior to any urine tests being performed leaving 187 patients in this study. Dipstick urine tests were not performed or not recorded for eight women at the 16-week gestation visit and 25 women at the 28-week gestation visit. A dipstick result at either visit was available on 187 women as all patients had at least one fasting dipstick test performed. Dipstick results were performed for 91 women at a routine clinic visit in the third trimester. Patient demographics are shown in Table 1.

Table 1. Patient demographics.

		Number (%)
Age at delivery (years)	20–25	15 (8%)
	25–30	38 (20%)
	30–35	84 (45%)
	35–40	39 (21%)
	>40	11 (6%)
Parity	0	67 (36%)
	1	80 (43%)
	2	23 (12%)
	3	10 (5%)
	≥4	7 (4%)
BMI (kg/m^2)	25–30	80 (43%)
	30–35	65 (35%)
	>35	42 (22%)
Ethnicity	Caucasian	163 (87%)
	Asian	10 (5%)
	Pacific Islander	5 (3%)
	Indian	3 (2%)
	Other	6 (3%)
GDM	Yes	21 (11%)
	No	166 (89%)

BMI: body mass index; GDM: gestational diabetes mellitus.

Ketone prevalence at 16 and 28 weeks gestation

Urine samples were obtained at a median of 15 weeks gestation (range 12–19 weeks) and 28 weeks gestation (range 24–29).

The overall rate of fasting ketonuria at 16 and 28 weeks gestation amongst the 187 women was 22%, with none of the women having ketonuria at both time points. The levels of ketonuria were variable but most women had only trace amounts of ketones in their urine. At 16 weeks gestation, 7% had trace amounts and 4% had small or higher amounts of urinary ketones. Similarly, at 28 weeks gestation when 162 women were assessed, 7% had trace amounts and 6% had small or higher amounts of urinary ketones. The proportion of women with moderate or greater levels of ketones was 2% of all participants at both 16 and 28 weeks gestation.

Prevalence at 36 weeks gestation

Random (fasting and non fasting) urine samples were obtained from routine clinic visits in the third trimester at a median of 36 weeks gestation (range 29–41). Eight percent of the 96 women tested had any detectable amount of ketones in their urine and 3% had small or more. No patients at 36 weeks gestation had a moderate or greater amount of urinary ketones.

Table 2. Reason for performing a urine test in the third trimester.

Reason for urine test	Ketonuria (*N*)	No ketonuria (*N*)
Contractions	5	23
Vomiting	4	1
Presyncope	4	1
Hypertension	4	12
Spontaneous rupture of membranes	3	16
Decreased fetal movements	2	26
Headache	0	7
Other	4	13
Routine clinic visit	11	161

The presence of ketonuria at any time point in the pregnancy did not correlate with BMI, age parity, ethnicity or a diagnosis of GDM.

Assessment of ketonuria in the third trimester

Two hundred and ninety-seven random urine tests were performed on 135 women in the third trimester: 172 at routine clinic reviews and 125 for a specific clinical indication. When performed at routine clinic reviews, only 6% had trace or more of ketones. When performed for a specific clinical indication 21% urine tests had trace or more of ketones. Ketonuria was significantly increased in women undergoing tests for clinical indications ($p < 0.01$). These 26 positive results in women tested for a specific clinical indication came from 24 women, 16 (67%) of whom had no ketonuria at either their 16, 28 or 36 week routine clinic visit. The indications for having a urine test in the third trimester are shown in Table 2 along with the presence or absence of

ketonuria and the degree of ketonuria. None of the women with hypertension with ketonuria were on antihypertensive medication at the time of the urine collection. Of the women with hypertension without ketonuria, two women were on labetolol and the remainder were not on any anti-hypertensive treatment.

Discussion

The results of this study show that ketonuria is a common finding in pregnancy. Twenty-two percent of women had ketones present in the fasting urine at either 16 or 28 weeks gestation and 8% had ketones in the non fasting routine clinic visit assessment at 36 weeks gestation. This falls in the range of previously reported prevalence rates ranging from 5% to 89%.[6,7] The large variability in the previously reported prevalence rates may be explained by the heterogeneity in study design and population of the studies. One study measured ketone levels only once at term and found a prevalence of 9%[9] while another measured ketones every 3–4 days from the end of the first trimester and found a prevalence of 89%.[6] This indicates that ketonuria may vary throughout pregnancy which is supported by our results. While the overall rates of ketonuria were similar at 16 and 28 weeks in our study, ketonuria was detected in different individuals at both timepoints. Previous studies also had different patient characteristics. One study included only women with GDM who tested their urine three times weekly from 28 weeks gestation and found a prevalence of 5%.[7] Another included women with any form of diabetes in pregnancy who tested their urine at any time in the last 24 h of pregnancy and had a prevalence of 57%.[7,10] Two studies of post-term pregnancies excluded all women with diabetes and had prevalence rates of 11% and 9%.[1,9] None of these studies required women to be fasting at the time of urine testing. In our study the presence of ketonuria did not correlate with a diagnosis of GDM. This finding is in keeping with a previous study that found that GDM was not associated with an increased propensity to ketosis with fasting.[11]

Our study only included women with a BMI of 25 or higher and this may have reduced the rates of ketonuria: outside pregnancy, overweight and obese people do not develop ketosis and ketonuria as rapidly in starvation as individuals of normal or underweight BMI.[12,13] Studies of the rate of ketonuria outside of pregnancy are limited. A Korean study found a prevalence of ketonuria of 11.8% in non-pregnant women after an 8-h fast.[13] Our findings of 22% in pregnancy support the theory that ketone production is accelerated in pregnancy.

The rate of ketonuria at 36 weeks gestation was not higher than the rate at 16 and 28 weeks gestation. Ketogenesis is more pronounced in the third trimester, likely secondary to increased maternal lipid metabolism.[4,14] Given this, one would have expected an increase in urinary ketone levels as pregnancy progressed. The lack of increased prevalence in this study may be due to the fact that urine samples collected at 16 and 28 weeks were collected after a fast of between 9.5 and 12 h whereas this was not the case at 36 weeks. Alternatively it is possible that although there is an increase in ketogenesis in the third trimester, there may be an increase in the uptake of ketones in the maternal brain and heart meaning that the rates of ketonuria do not increase. To our knowledge no previous studies have addressed this question.

We found that maternal ketones were significantly more likely to be elevated if there was a specific clinical indication for performing a urine test. This raises the possibility that urinary ketones are a marker of maternal pathology and potentially it is this pathology that causes adverse fetal outcomes rather than maternal ketones themselves.

Some previous studies that found an association between maternal ketones and adverse pregnancy outcomes corrected for patients with an acute change in their physiology, however the majority of studies did not. One study that found a correlation between maternal ketones and oligohydramnios, fetal heart rate decelerations and non-reactive non-stress tests excluded women who were vomiting or had diarrhoea, hypertension, a history of renal disease or a high risk pregnancy.[9] Urine specific gravity was also used as a marker of dehydration and was not found to be associated with ketonuria. Another study with similar outcomes excluded women with high risk pregnancies such as renal disease or hypertension and also found no association between ketonuria and urine specific gravity.[1] However, in the studies evaluating maternal ketones and low childhood IQ, there was no correction for maternal pathology.[2,10,15–19] It is possible therefore that an acute maternal pathology was present at the time of testing for maternal ketones, resulting in both elevated ketones and an adverse fetal environment.

The strengths of this study include that women were tested for the presence of urinary ketones at different time points throughout the pregnancy. In the third trimester the reason for the urine test was documented allowing analysis of the effect of the clinical indication on the test result. The methodology for urine collection between the 16 and 28 week gestation visit, and the 36 week gestation visit differed with the measurements at 36 weeks not necessarily collected in the fasting state. This may have decreased the prevalence of ketonuria at 36 weeks gestation.

A better understanding of ketones in normal pregnancy is crucial in order to understand the association between maternal ketones and adverse pregnancy outcomes. Ideally such studies would measure serum beta-hydroxybutyrate levels as adverse effects from maternal ketones will be via serum ketones rather than urinary ketones. We need to be able to better inform our patients about the potential effects of elevated ketones in pregnancy and particularly the risks related to starvation, avoidance of meals and low-carbohydrate diets. Further research needs to be undertaken to evaluate the impact of elevated ketones in pregnancy.

Summary

Urinary ketones are common in pregnancy. This study shows that 22% of women have urinary ketones at either 16 or 28 weeks gestation and 8% have ketones at 36 weeks gestation. In some previous studies, maternal ketonuria has been associated with adverse fetal outcomes. Our finding that ketonuria is more common if a woman has a clinical indication for having a urine test performed raises the possibility that ketonuria is associated with adverse pathology. Potentially it is this pathology that leads to adverse fetal outcomes rather than the ketones themselves. More studies need to be performed to evaluate the prevalence of elevated maternal ketone levels and the risks of such elevated levels in pregnancy.

Acknowledgements

The authors would like to thank the SPRING participants; the SPRING trial group: Katie Foxcroft, Anne Tremellen, Prof H David McIntyre, Sharney Grant, Dr Jacinta Tobin, Dr Shelley Wilkinson, Dr Chris McSweeney, Prof Peter O'Rourke and Dr Barbara Lingwood.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: The SPRING study has received probiotics and placebo products from Chr Hansen A/S. The authors have no other conflicts of interest to disclose.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: HLR is supported by a Royal Brisbane and Women's Hospital Foundation postgraduate research fellowship. HLB is supported by the Skip Martin Research Fellowship from the Australian Diabetes Society. The SPRING study is supported by the National Health & Medical Research Council (grant# 1028575) and the Royal Brisbane and Women's Hospital Foundation.

Ethical approval

Ethics approval was granted from the Royal Brisbane and Women's Hospital Human Research Ethics Committee, HREC/11/QRBW/467. All women gave written informed consent prior to enrolment in the SPRING study.

Guarantor

Helen Robinson is the guaranteeing author and guarantee's the manuscript's accuracy and contribution of all co-authors.

Contributorship

Helen Robinson designed the study, collected the data, analysed the data and wrote the manuscript. Helen Barrett designed the study and reviewed the manuscript. Katie Foxcroft collected the data and reviewed the manuscript, Leonie Callaway designed the study and reviewed the manuscript. Marloes Dekker Nitert designed the study, analysed the data and reviewed the manuscript.

References

1. Onyeije CI and Divon MY. The impact of maternal ketonuria on fetal test results in the setting of postterm pregnancy. *Am J Obstet Gynecol* 2001; 184: 713–718.
2. Churchill JA and Berendes HW. Intelligence of children whose mothers had acetonuria during pregnancy. *Perinat Factors Affecting Hum Dev* 1969; 185: 30–35.
3. Rudolf MC and Sherwin RS. Maternal ketosis and its effects on the fetus. *Clin Endocrinol Metab* 1983; 12: 413–428.
4. Herrera E. Lipid metabolism in pregnancy and its consequences in the fetus and newborn. *Endocrine* 2002; 19: 43–55.
5. Metzger BE, Ravnikar V, Vileisis RA, et al. ''Accelerated starvation'' and the skipped breakfast in late normal pregnancy. *Lancet* 1982; 1: 588–592.
6. Chez RA and Curcio FD 3rd. Ketonuria in normal pregnancy. *Obstet Gynecol* 1987; 69: 272–274.
7. Major CA, Henry MJ, De Veciana M, et al. The effects of carbohydrate restriction in patients with diet-controlled gestational diabetes. *Obstet Gynecol* 1998; 91: 600–604.
8. Nitert MD, Barrett HL, Foxcroft K, et al. SPRING: an RCT study of probiotics in the prevention of gestational diabetes mellitus in overweight and obese women. *BMC Pregnancy Childbirth* 2013; 13: 50.
9. Hamdi K, Bastani P, Gafarieh R, et al. The influence of maternal ketonuria on fetal well-being tests in postterm pregnancy. *Arch Iran Med* 2006; 9: 144–147.
10. Churchill JA, Berendes HW and Nemore J. Neuropsychological deficits in children of diabetic mothers. A report from the Collaborative Sdy of Cerebral Palsy. *Am J Obstet Gynecol* 1969; 105: 257–268.
11. Buchanan TA, Metzger BE and Freinkel N. Accelerated starvation in late pregnancy: a comparison between obese women with and without gestational diabetes mellitus. *Am J Obstet Gynecol* 1990; 162: 1015–1020.
12. Mohammadiha H. Resistance to ketonuria and ketosis in obese subjects. *Am J Clin Nutr* 1974; 27: 1212–1213.
13. Joo NS, Lee DJ, Kim KM, et al. Ketonuria after fasting may be related to the metabolic superiority. *J Korean Med Sci* 2010; 25: 1771–1776.
14. Persson B. Newborn fuel homeostasis and metabolic abnormalities in ifants of diabetic mothers. *Mead Johnson Symp Perinat Dev Med* 1978; 45–52.
15. Naeye RL and Chez RA. Effects of maternal acetonuria and low pregnancy weight gain on children's psychomotor development. *Am J Obstet Gynecol* 1981; 139: 189–193.
16. Persson B and Gentz J. Follow-up of children of insulin-dependent and gestational diabetic mothers. Neuropsychological outcome. *Acta Paediatr Scand* 1984; 73: 349–358.
17. Stehbens JA, Baker GL and Kitchell M. Outcome at ages 1, 3, and 5 years of children born to diabetic women. *Am J Obstet Gynecol* 1977; 127: 408–413.
18. Rizzo T, Metzger BE, Burns WJ, et al. Correlations between antepartum maternal metabolism and child intelligence. *N Engl J Med* 1991; 325: 911–916.
19. Silverman BL, Rizzo TA, Cho NH, et al. Long-term effects of the intrauterine environment. The Northwestern University Diabetes in Pregnancy Center. *Diabetes Care* 1998; 21: B142–149.