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The Influence of Maternal Ketonuria on Biophysical Fetal Test Results in the Evaluation of Postterm Pregnancy

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Abstract

Background The perinatal morbidity and mortality increase significantly as pregnancy progresses beyond term. The ketone production as a result of dehydration becomes significant in the latter portion of pregnancy.

Objective To determine whether ketonuria, a commonly assessed urinary marker of maternal starvation and dehydration, is associated with abnormal fetal test results in the setting of postterm pregnancy.

Methods During a one-year period (March 2007-March 2008), a total of 180 visits of 100 patients of postterm pregnancies (≥ 41 weeks' gestation) occurred at Baghdad Teaching Hospital. Maternal assessment included vital signs and urinalysis. The presence and degree of maternal ketonuria was correlated against abnormal results of fetal heart rate tests, non stress tests, amniotic fluid index measurements (the biophysical profile scores) performed on the same day.

Results There were 180 evaluations suitable for inclusion in the study. Clinically detectable ketonuria occurred in 13.9% of the patients studied. Patients with clinically detectable ketonuria were at increased risk relative to patients without ketonuria for abnormal outcomes during postterm testing, including the presence of oligohydramnios (28% vs. 9.7%; p <0.018), non reactive non stress tests (12% vs. 2.6%; p <0.03), and variable, late fetal heart rate decelerations (20% vs. 8.3%; p <0.05).

Conclusions Maternal ketonuria among patients with postterm pregnancy was associated with a >2 fold increase in the occurrence of oligohydramnios, a 3-fold increases in non reactive non stress tests, and a significant increase in fetal heart rate decelerations.

Key words maternal ketonuria; biophysical fetal test; postterm pregnancy

Introduction

Postterm pregnancy: A pregnancy which has gone beyond 42 weeks or 294 days from the first day of the last menstrual period (LMP) [1].

The incidence of postterm pregnancy varies from 3% to 10 %[2,3]. The retrospective studies indicate that there is an increased risk of perinatal mortality after 42 weeks [4]. The presumed pathogenesis of the complications associated with post date pregnancy relates to progressive uteroplacental insufficiency. As gestational age advances, uteroplacental insufficiency leads to fetal asphyxia, oligohydramnios, meconium aspiration, and in severe cases fetal central nervous system damage and death [5,6].

The mainstay of antenatal management lies first in the diagnosis of postterm pregnancy. Once diagnosed the pregnancy can be terminated by induction of labor or managed conservatively until spontaneous onset of labor. Whilst awaiting spontaneous onset of labor, fetal well being should be monitored by appropriate available tests as non stress test, biological profile test, Amniotic Fluid Index [A.F.I].

Ketonuria: The increased excretion of ketone bodies in the urine higher than 1mg/24h. known as ketonuria which resulted from the

excessive formation of ketone bodies that results in increased blood levels (ketonemia).The overall condition is called ketosis [7,8].

The metabolism in normal pregnancy is characterized by more exaggerated excursions in maternal nutrient fuels and rapid development of ketonemia during fasting, a pattern described as "accelerated starvation"[9, 10].

The changes in accelerated starvation, a more rapidly evolving decline in glucose and increases in free fatty acids and β-hydroxybutyrate during fasting than occurs outside of pregnancy, are thought to be mediated by the increased nutrient flux to the fetus and by the secretion of hormones that exert lipolytic and anti insulin action, such as human placental lactogen and prolactin [11].

Methods

A prospective study was carried out at Baghdad Teaching Hospital, (Medical City Hospital) for the period from 1st March 2007 to 1st of March 2008.

During the study period, 180pregnancy evaluations were performed on 100postterm pregnant women ≥ 41 weeks' gestation according to last menstrual period and early ultrasonography. They were selected from antenatal clinics and they were followed up to the time of the delivery.

Eight patients were excluded from further analysis, one patient had gestational diabetes, and three patients had other high risk pregnancy complications, such as hypertension or renal disease. Three patients were with late registration for antenatal care or with an uncertain gestational age.

The protocol used for expectant management for those postterm pregnant women has been published elsewhere. After the initial visit antenatal assessment was continued in these cases on a twice weekly basis.

A complete obstetrical and medical history was taken from each patient with special attention for the last menstrual period.

The Expected date of delivery (EDD) that was calculated from the menstrual history was confirmed by an ultrasound examination performed between 12 and 20 weeks of gestation. The maternal assessment also consisted of vital signs, blood pressure, temperature, pulse rate, body weight, height, and urinalysis.

Measurement of ketonuria:

Urinalysis was performed with a Combi-Urine test strips (Panreac. QuimicaA, Company Head Office: Barcelona) that simultaneously evaluated urinary glucose, urobilinogen, ketones, pH, protein, and specific gravity. Assessment of ketonuria with this product used the nitroprusside reaction technique and yielded a semi-quantitative reading of urinary acetoacetic acid concentration. The nitroprusside reaction is a sensitive assay for ketone bodies in urine. Values of ketonuria, as assessed with Combi-Urine test ranged from negative to large. Each patient thus had 1 of the following 4 possible values recorded for ketonuria: negative, 0 mg/dl; small, 1 to 30 mg/dl; moderate, 30 to 40 mg/dl; and large, >40 mg/dl.

Procedure:

The urine used for the analysis was fresh, uncentrifuged and collected in clean containers, free of detergents. The test strip was immersed in the urine for approximately 2 seconds. The reagent areas on the strip were compared with corresponding color chart on the container about 60 seconds after immersion.

Fetal assessment included non-stress test (NST), ultrasonographic determination of the amniotic fluid index (AFI) and biophysical profile (BPP).

- Non-stress test: NST result was considered abnormal in the presence of recurrent fetal heart rate (FHR) variable decelerations, late decelerations or 120 min. of non reactivity.
- Amniotic Fluid Index: AFI was quantified by means of the four-quadrant method described by Phelps et al, (1999). Oligohydramnios was defined as AFI<5.1 cm.

- Biophysical profile: (BPP) was considered normal if the score was 8 or more, including normal amount of liquor. In the presence of the oligohydramnios, an abnormal FHR tracing, patients were referred for labor induction. Patients with normal fetal test results were assessed twice weekly until abnormal results were obtained or spontaneous labor occurred.

Statistical analysis

Data were collected, arranged and tabulated in a number, percentage for discrete variables and mean±SD for continuous variables. Data were checked and transferred to a personal computer using SPSS 7.5 (Statistical Package for Social Science) and format for statistical analysis association between different variable were measured by using student t-test, fisher exact probability test. *p* value of <0.05 was considered to be significant.

Results

During the study period, 180 urinalyses were performed on one hundred patients, their age ranged between (19-42) years and parity (0-6). A mean of 1.8 evaluations per patient was performed (range, 1-3 evaluations per patient). Twenty-five evaluations showed some degree of ketonuria and one hundred fifty-five showed no ketonuria, for an overall incidence of ketonuria of 13.9% in this population. Most patients with ketonuria had relatively minor levels of ketone bodies in the urine (Table 1).

Table 1. The distribution of ketonuria in the study

Parameter	Degree of ketonuria				Total
	No ketone	Small ketones	Moderate ketones	Large ketones	
No. (%)of women	155(86.1%)	13(7.2%)	7(3.9%)	5(2.8%)	180(100%)
Total	155(86.1%)	25(13.9%)			180(100%)

Demographically, the mean age of patients with ketonuria±S.D was 26.28±6.47 years and in patients with no-ketonuria was 27.08±5.45 years. There were no statistically significant differences regarding their mean age (Table 2).

Table 2. Maternal demographic parameters

Parameter	Ketonuria Group (n=25)	No ketonuria Group (n=155)	Statistical Significance
Mean maternal age ±S.D	26.28±6.47	27.08±5.45	*P*=0.506
Nulliparous no. (%)	12(48%)	73(47.1%)	*P*=0.155
Mean Parity ±S.D	1.24±1.65	1.2±1.7	*P*=0.078
Mean height (in) ±S.D	63.67±1.55	63.38±5.06	*P*=0.779
Mean weight (kg) ±S.D	86.20±8.22	82.52±12.04	*P*=0.142

Our bedside assessments for evidence of maternal dehydration, a potential contributor to maternal ketonuria, reveal a significant difference in mean urine specific gravity between patients with and without ketonuria, where the mean urine specific gravity was 1.18 ±0.80 in patients with ketonuria and 1.01±0.007 in patients without ketonuria. The *p* value was less than 0.011 (Table 3).

Table 3. Comparison in urine specific gravity between patients with and without ketonuria

Parameter	Ketonuria group (n=25)	No ketonuria group (n=155)	Statistical significance
Mean urine specific gravity ±S.D	1.18±0.80	1.01±0.007	*p* <0.011

The mean amniotic fluid index ±S.D (8.69±4.47 cm) was statistically lower in patients with ketonuria than in patients without ketonuria (10.50±4.24 cm; Table 4). This observation of an association of diminished amniotic fluid volume with ketonuria remained significant after patients were stratified according to degree of ketonuria. The *p* value was less than 0.05 (Figure 1).

Table 4. Antenatal testing outcomes

Parameter	Ketonuria group(n=25)	No ketonuria group(n=155)	Statistical significance
Mean AFI±S.D	8.69±4.47	10.50±4.24	*p*<0.05
Oligohydramnios no. (%)	7(28.0%)	15(9.7%)	*p*<0.018
Spontaneous FHR deceleration no. (%)	5(20%)	13(8.3%)	*p*<0.05
Non reactive NST no. (%)	3(12.0%)	4(2.6%)	*p*<0.03
Mean BPP ±S.D	8.80±1.15	9.40±7.46	*p*<0.69

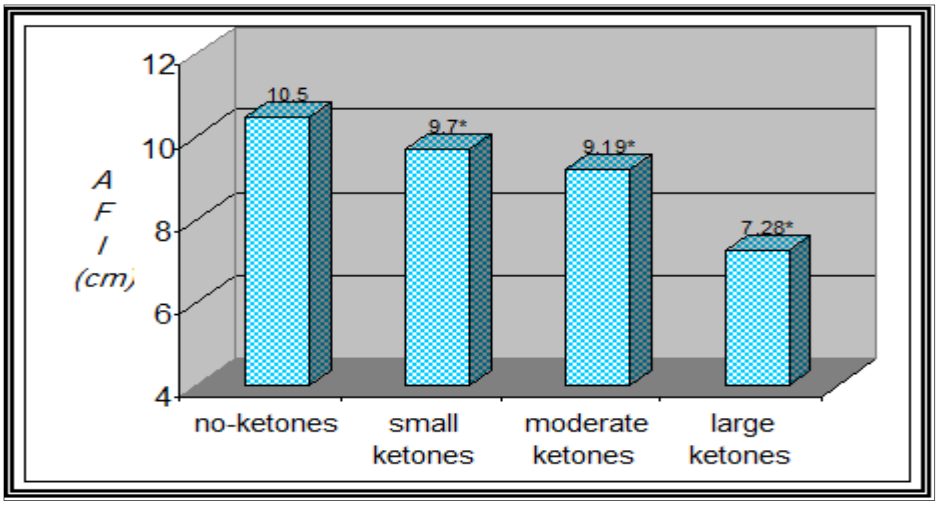

Figure 1. Average amniotic fluid index (AFI) according to degree of ketonuria. Asterisk, *p*<0.05, versus no ketones

To determine the clinical significance of the effect of ketonuria on amniotic fluid volume, we also compared the frequencies of oligohydramnios between patients with and without ketonuria. Our results indicate a >2 fold increase in the incidence of oligohydramnios among patients with ketonuria (28%) relative to those without ketonuria (9.7%). The *p* value was less than 0.01 (Table 4). Furthermore; the incidence of oligohydramnios was directly related to the degree of ketonuria. The highest incidence of oligohydramnios was (60%) occurred among patients with large ketonuria, whereas the lowest incidence was (9.7%) occurred among patients without ketonuria, which was statistically significant (*p* <0.004; Figure 2).

The incidence of oligohydramnios in patients with moderate ketonuria was (28.6%) and in patients with small ketonuria was (15.4%), both were significantly different when compared with patients without ketonuria (p <0.01; Figure 2).

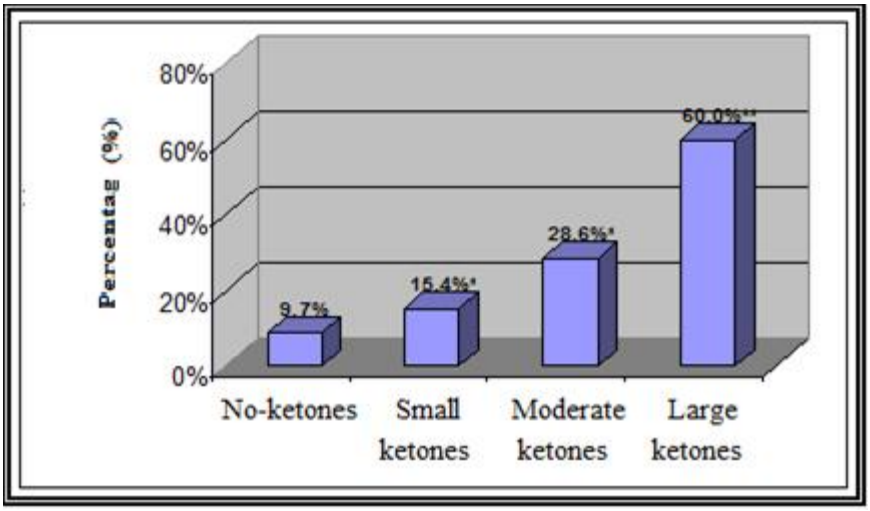

Figure 2. Percentages of patients with oligohydramnios according to degree of ketonuria. Asterisk, p <0.01, versus no ketones; 2asterisks, p <0.004, versus no ketones

When patients were stratified according to amniotic fluid index, it was found that; the highest incidence of ketonuria was (31.8%) occurred among patients with oligohydramnios which was more than twice as likely to have ketonuria as were patients with any other level of amniotic fluid volume (Figure3).

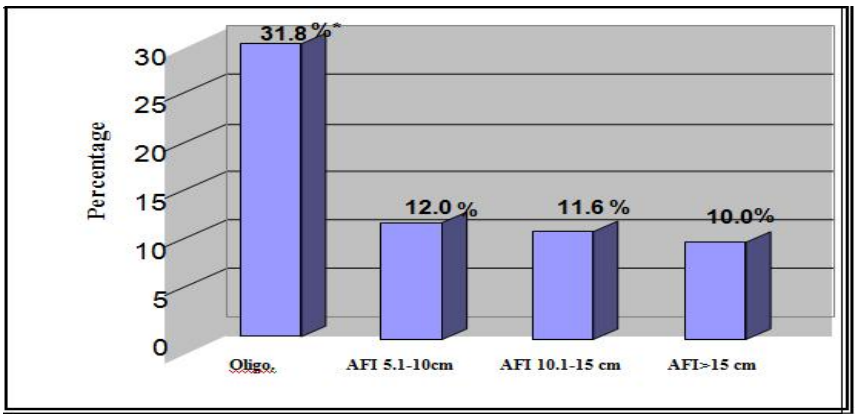

Figure 3.Percentages of patients with ketonuria according to AFI categories. Asterisk, p <0.05, versus any other group.Oligo, oligohydramnios

Spontaneous Fetal Heart Rate(FHR) decelerations were also more common among patients with ketonuria(20%) than among patients without ketonuria (8.3%), which was statistically significant (p<0.05; Table 4).No statistical association was found between the degree of ketonuria and the presence of FHR decelerations(Table 5).

Table 5. Percentages of patients with FHR decelerations and non reactive Non-stress test $(NST)_s$ according to degree of ketonuria (small, moderate, large ketones; *p* value, versus no ketones)

Parameter	Degree of ketonuria								*p* value
	No ketones (n=155)		Small ketones (n=13)		Moderate ketones (n=7)		Large ketones (n=5)		
	No.	%	No.	%	No.	%	No.	%	
Spontaneous FHR decelerations	13	8.3	3	23.0	1	14.3	1	20.0	>0.05
Non reactive NST_s	4	2.6	1	7.7	1	14.3	1	20.0	<0.05

Patients with ketonuria were statistically more likely to have non reactive NST_s [(12.0%) vs. (2.6%); *p* <0.03, table 4]. Patients with large ketonuria were almost 7 times more likely to have non reactive NST_s than were those without ketonuria (20% vs. 2.6%; *p* <0.03, Figure4).

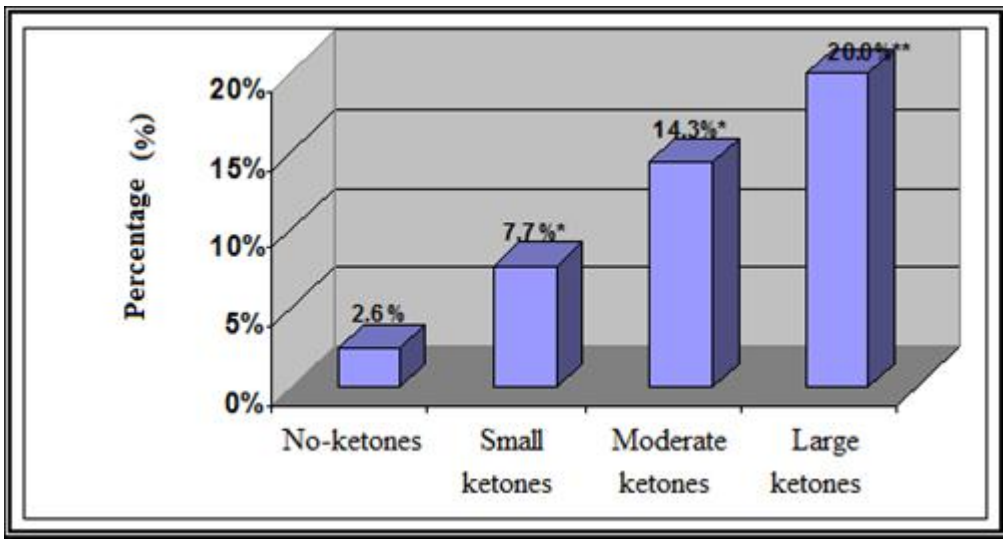

Figure 4. Percentages of patients with non-reactive NST_saccording to degree of ketonuria. Asterisk, *p* <0.05, versus no ketones; 2 asterisks, *p* <0.03 versus no ketones

Discussion

Perinatal morbidity and mortality increase significantly as pregnancy progresses beyond term [12]. Approximately 18.5% of all pregnancies continue to >41 weeks' gestation and 4% to 10% continue to >42 weeks [13]. Although the risks associated with prolonged pregnancy have been chronicled, the management of this common condition remains controversial. The process of enhanced ketone production as a result of accelerated starvation or dehydration becomes significant in the latter portion of pregnancy [14].

Decreased Amniotic Fluid Index In our study the mean amniotic fluid index±SD (8.69±4.47 cm) was lower in patients with ketonuria than in patients without ketonuria (10.5 ±4.24 cm). This association of diminished amniotic fluid volume with ketonuria remained significant after patients were stratified according to degree of ketonuria (Figure1), and it was also found that, the highest incidence of ketonuria (31.8%) occurred among patients with

oligohydramnios which was more than twice as likely to have ketonuria as were patients with any other level of AFI (Figure 3).

It was found that the maternal ketonemia resulting in ketonuria, is a hyperosmolar condition [15]. The maternal condition involving hyperosmolarity, such as maternal dehydration, result in a diminution in fetal amniotic fluid volume from decreased fetal urination [16].These studies provide preliminary evidence to support the hypothesis that ketone bodies passed from the mother to the fetus may elicit alterations in amniotic fluid volume and FHR reactivity.

Our results could be also explained by other studies on the relationship between the maternal fluid volume and the amniotic fluid volume, which demonstrated an increase in the amniotic fluid volume in response to maternal hydration [17-19].

It was found that maternal oral hydration increased the AFI by approximately 16% where as fluid restriction decreased the AFI by 8% in women with normal amniotic fluid. These findings support previous data that maternal hydration increased the AFI by 31% in women with decreased amniotic fluid and suggest that maternal fluid volume or osmolality may have a role in maintaining the amniotic fluid volume [17].

Abnormal FHR tracing: As shown in the result of our study spontaneous FHR decelerations were more common among patients with ketonuria (20%) than among patients without ketonuria (8.3%), and it was more likely to have non reactive NST_s (12%) than were those without ketonuria (2.6%). The association of ketonuria and non reactive NST_s increased directly with each increment of increasing ketonuria (Table 5, Figure 4) patients with large ketonuria were 7 times more likely to have non-reactive NST_s than were those without ketonuria. This could be explained by one of the followings:

- One of the most commonly documented fetal physiologic alterations resulting from exposure to ketone bodies involves the neurologic system [20-24]. Bhasin et al (1982), found that synthesis of pyrimidines in the fetal brain decreases significantly in the presence of ketone bodies. This is seen as an attempt by the fetus to reduce its' metabolic demands and conserve energy in the face of possible maternal nutritional deprivation [20].
- It was hypothesized that the presence of a non reactive NST is an early manifestation of these neurologic alterations in some fetuses exposed to maternal ketone bodies. Support for this hypothesis is provided by the fact that the response (FHR non-reactivity) appears to be dose related to the degree of ketonuria (Figure 4). Other support for this concept is provided by previous studies that have documented FHR abnormalities in the presence of extreme quantities of ketone bodies such as those seen in diabetic ketoacidosis[25,26]. Alternatively, it is possible that maternal ketonuria is a marker for maternal dehydration and hypovolemia. Subsequent fetal hypovolemia could explain both FHR changes and decreased amniotic fluid volume.

It was a small study, the relatively small number of patients in the groups with moderate (n=7) and large (n=5) ketonuria may have reduced our ability to generalize with respect to the frequency of specific outcomes in these groups. It should be noted, however, that statistically significant relationship between fetal test results and degree of ketonuria existed regardless of the exact cutoff level used to define the severity of ketonuria. Although the maternal ketonuria is a reversible condition [25], it is impossible from this study to determine whether the oligohydramnios and FHR abnormalities found in patients with ketonuria represented reversible alterations in fetal test results or additional evidence in support of the need for immediate delivery.

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