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Maternal Ketonuria and Results of Fetal Testing in the Impending Post-Term Pregnancy

Wafaa S. Abd-Alamieer *CABOG*, **Intedhar N. Farak** *MBChB*

Dept. of Obstetrics and Gynecology, Al-Kadhimiya Teaching Hospital, Baghdad, Iraq

Abstract

Background The observation of ketonuria and its severity in post- term pregnancies can be considered as one of the most important biochemical markers, which can help the obstetrician to predict the adverse outcome of post-term pregnancy with some sort of precision.

Objective To assess the effect of maternal ketonuria on fetal wellbeing in pregnant woman with post-term pregnancy, estimate the frequency of amniotic fluid volume changes in different degrees of ketonuria and to estimate the frequency of non-stress test abnormalities according to the severity of ketonuria.

Methods Two hundred and fifty post-term pregnant women divided into pregnant woman with ketonuria of different severity (27) and pregnant woman without ketonuria (223). Ketone bodies were tested in urine. Fetal testing had been done for all of them in terms of non stress test and amniotic fluid volume assessment in term of amnioticfluid index.

Results Ketonuria was found in 10.8% of post-term pregnant woman and 62.9% of them had moderate to severe ketonuria. Oligohydramnios had been observed in 62.9% and 22.4% of pregnant woman with ketonuria and those without ketonuria, respectively. 4(80%) with severe ketonuria had oligohydramnios. Abnormal non-stress test was observed in 85.1% and 45.7% of those pregnant women with and those without ketonuria, respectively. There is a significant statisticalassociation between the presence of ketonuria and the result of fetal testing.

Conclusion Ketonuriawas significantly associated with oligohydramnios and abnormal results of non-stress test. Higher frequency of oligohydramnios and abnormal results of non-stress test among those with severe ketonuria.

Keywords Post-term, ketonuria, oligohydramnios, non-stress test

Introduction

Ketonuria is a medical condition in which the ketone bodies are present in excess in the urine as an indication that it is using an alternative source of energy, the production of Ketone bodies is a normal response to a shortage of glucose, meant to provide an alternate source of fuel from fatty acid [(1)]. Several previous studies have shown that ketones elicit alteration in the amniotic fluid volume of human beings [(2)]. By this effect on the amniotic fluid volume and composition as well as on the general wellbeing of the fetus, Ketonuria and its degree can be proposed as a biochemical marker that might augment the accuracy of the decision in addition to other parameters included in the classic and modified biophysical profile. Ketonuria during pregnancy is commonly a transient phenomenon and has a negligible effect on maternal and fetal outcome,

but in a prolonged pregnancy, the prolonged exposure to the ketone bodies and possible higher production rate of them, might result in more adverse outcome[3].

Post-term or prolonged pregnancy is our preferred expression for an extended pregnancy [4]. Post maturity is a neonatal diagnosis and should be used to describe the infant with recognizable clinical features associated with peeling, parchment-like skin, meconium staining of the skin, membranes and the umbilical cord. In addition, these infants may have overgrown nails, well-developed creases on the palms and soles, abundance of scalp hair, little vernix or lanugo hair, scaphoid abdomen and minimal subcutaneous fat [5].

Pathology of ketonuria is gradual deterioration in oxygen supply and nutrition can be tolerated for some while by reducing the metabolic demand and oxygen requirements and by increasing hematocrit and catecholamine. Chronic hypoxemia associated with placental insufficiency in post-term pregnancy may develop with noticeable changes in fetal heart rate, or other biophysical activities until they become sufficient to result in academia. A reduction in the metabolic rate accompanied reduced oxygen delivery and reduced carbohydrate and fat storage will precede the onset of anaerobic metabolism and increase chance of development of academia [6]. A reactive non stress test is define as 2 or more fetal heart rate acceleration at least 15 beat/minute above the baseline and lasting at least 15 seconds within 20 minutes period [7].

Amniotic fluid changes during pregnancy, at 22 weeks; the average amniotic fluid volume is 630 ml and this increase in amount to 770 ml at 28 weeks. Between 29 and 37 weeks, there is little change in volume; the average is 800 ml. beyond 39 weeks, the amniotic fluid volume decrease sharply in amount to 515 ml at 41 weeks. Once a pregnant woman became post-date, there is a 33% decline in amniotic fluid volume/week, consistent with clinical observation of an increased incidence of oligohydramnios in post-term gestation [5].

The objectives of this study was to assess the effect of maternal ketonuria on fetal wellbeing in pregnantwoman with post-term pregnancy, estimate the frequency of amniotic fluid volume changes in different degrees of ketonuria and to estimate the frequency of non-stress test abnormalities according to the severity of ketonuria.

Methods

This cross sectional study was carried out at Al-Kadhiymia Teaching Hospital in the Department of Obstetrics and Gynecology during the period from 1st of January 2012 to 31th of October 2012. Two hundred and fifty post-date pregnant women were recruited from outpatient clinics and hospital admissions. They weredivided into two groups:

1. Group A: 223 pregnant women without ketonuria.
2. Group B: 27 pregnant women with ketonuria of different severity.

An informed verbal consent was obtained from all women included inour study. A full medical and obstetrical history and examination were done for each candidate. The exclusion criteria in our study were: Any previous history of diabetes, hypertension, vascular disease, heart disease, collagen disease, renal disease, and smoking, Obesity (body mass index more than 30 kg/m^2), unsure date of last menstrual period and no early ultrasound report, history of drug use.

The characteristics of patients participated in our study were singleton uncomplicated pregnancy without gross congenital anomalies, gestational age more than 40 week, not in labor, intact membrane.

Maternal investigation for the presence or absence of ketone bodies in the urine, amniotic fluid index and non-stress test were performed on the same day. The biochemical estimation of ketonuria was done when 3 ml of freshly voided urine was collected in a clean dry container and then centrifuged for 2 minutes in macro centrifuge machine, Bayer reagent strip (KETOSTIX), which is specific for acetoacetic acid

detection in urine. The strip color was compared with the standard color block on the bottle label to determine the presence or absence of ketonuria and its degree if present. The results were either: light pink colors (no ketone bodies), pink (mild ketonuria), and one plus=15 mg/dl, dark pink (moderate ketonuria), 2 plus=40 mg/dl, violate (severe ketonuria), 3 and 4 plus=80-160 mg/dl.

Real time ultrasound was performed to measure the amniotic fluid index for each pregnant woman, an amniotic fluid index of less than 5 cm was regarded as oligohydramnios, thereafter, and non-stress test was done for each pregnant women. This was performed by cardio-tocography at the labor ward.

Statistical analysis for the association between maternal ketonuria and fetal test results was made. Data were collected and analyzed using computer facility programs, statistical package for social sciences (SPSS) version 16.0 for windows. The frequencies, percentages, means and standard deviation for variables were analyzed. Chi-square was used to detect the significant of relationship between various variables. Statistical significance was considered when P value less than 0.05.

Results

During the study period, a total of 250 post-term pregnant were included; 27 (10.8%) of them show different degree of ketonuria, 203 (89.2%) without ketonuria. Our study showed that out of the 27 pregnant women with positive ketonuria, 12 (44.4%) had moderate ketonuria, 10 (37.1%) had mild ketonuria, and 5 (18.5%) had severe ketonuria (Table1).

Table1. Patients' distribution according to the severity of ketonuria

Severity of ketonuria	No.	%
Mild	10	37.1
Moderate	12	44.4
Severe	5	18.5
Total	27	100

Statistical analysis comparing different demographic features of the pregnant women included in this study revealed no statistically significant difference between pregnant women with ketonuria and those without ketonuria in term of maternal age and parity (Table 2).

Table2. Maternal demographic parameters and their statistical significance.

Maternal demographic parameter	Ketonuria		*P* value
	present (n=27)	absent (n=223)	
Age(years)	27.7±6.4	27.4±6.7	>0.05
Primigravida	44.5%	34.5%	>0.05

Of pregnant women with ketonuria, 16 (59.3%) had passed the 41week of gestation. Thirteen out of 16 pregnant women with moderate to severe ketonuria had passed the 41week of gestation (81.2% of those with moderate to severe ketonuria) including 4 (80%) with severe ketonuria and 9 (75%) with moderate ketonuria (Table3).

Amniotic fluid index (AFI) in those pregnant women with ketonuria ranged between 1 and 8 (mean±SD= 4.8±1.8), while it was between1-19 (mean±SD = 9.4±4.8) in those with no ketonuria. This study indicated that 17 pregnant women with ketonuria (63% of the sample) had an AFI ofless than 5 i.e. oligohydramnios, on the other hand only 50 pregnant women with post-term pregnancy without ketonuria had oligo-hydramnios (22.4% of the sample). Furthermore, 80% of those with severe ketonuria (4 pregnant women) had oligohydramnios.

Statistical analysis revealed that there was a statistically significant difference in thevalue of AFI between those with and those without ketonuria, (P<0.001) (Table 4).

Regarding the results of non-stress test (NST), our study showed that non-stress test was abnormal in 23 pregnant women (85.1%) with ketonuria and post-term pregnancy, whether this abnormality was in terms of spontaneous

deceleration in the fetal heart rate in 10(37%) or in terms of non reactive NST 13 (48.1%). In contrast, 121 pregnant women (54.3%) without ketonuria had reactive non stress test versus 99(14.8%) of those without ketonuria had abnormal non stress test.

In addition, this study shows that all the pregnant women with severe ketonuria (5 pregnant women) had abnormal non stress test, either in the form of spontaneous deceleration in the fetal heart rate (4 pregnant women, 80% of those with severe ketonuria) or in the form of non-reactive fetal heart (1 pregnant woman, 20% of those with severe ketonuria). Statistical analysis using chi-square test indicated that the presence of ketonuria in pregnant women with post-term pregnancy is associated with higher risk of having abnormal results of non stress test (P<0.05) (Table 5).

Table 3. Patients' distribution according to their gestational age

Gestational age	ketonuria						Total	
	Mild		Moderate		Severe			
	No.	%	No.	%	No.	%	No.	%
40thweeks	7	70	3	25	1	20	11	40.7
41thweeks	3	30	9	75	4	80	16	59.3
Total	10	100	12	100	5	100	27	100

Table 4. Patients' distribution according to their amniotic fluid index

Amniotic fluid index(cm)	Ketonuria present						Ketonuria Absent	
	Mild		Moderate		Severe			
	No.	%	No.	%	No.	%	No.	%
<5	5	50	8	66.7	4	80	50	22.4
5-9.9	5	50	4	33.3	1	20	67	30.1
10-14.9	0	0	0	0	0	0	60	26.9
15-19.9	0	0	0	0	0	0	46	20.6
Total	10	100	12	100	5	100	223	100
Range	1-8						1-19	
Mean ±SD	4.8±1.8						9.4±4.8	
Statisticalanalysis	P value < 0.001							

Table 5. Patients' distribution according to the results of non-stress test

Results of Non-stress test	Ketonuria present						Ketonuria Absent	
	Mild		Moderate		Severe			
	No.	%	No.	%	No.	%	No.	%
Spontaneous deceleration of fetal heart rate	2	20	4	33.3	4	80	36	16.1
Non-reactive	5	50	7	58.4	1	20	66	29.6
Reactive	3	30	1	8.3	0	0	121	54.3
Total	10	100	12	100	5	100	223	100
Statisticalanalysis	P value < 0.05							

Discussion

There are general consensuses that perinatal mortality and morbidity are increased several folds when pregnancies are prolonged especially beyond the 42 week of gestation so its management is a subject of concern [8].

Assessment of amniotic fluid has become an integral component in the ante-partum assessment of pregnancies which are at risk of fetal death. The amniotic fluid index and the largest vertical pocket are semi-quantitative ultrasonogrphic techniques used to estimate amniotic fluid volume [9].

Post-term pregnancy is a universally accepted indication for antenatal fetal monitoring [10,11]. Option for evaluating fetal wellbeing include non-stress testing with amniotic fluid assessment, the biophysical profile or modified biophysical profile, the oxytocin challenge test, or a combination of these modalities. There is some observational evidence that some pregnancies at risk of adverse outcome can be identified, but less evidence that the prediction of adverse outcome confers prevention [12]. No single method has been shown to be superior [10,11,13].

Ketonuria is a commonly assessed as a urinary marker of maternal starvation and dehydration [3]. These findings stimulate many researches workers to hypotheses that ketonuria in the setting of post-term pregnancy can have a potential effect on the fetal wellbeing which can be evaluated by assessing any possible relation between the presence of Ketonuria and its severity and the results of fetal testing including mainly non stress test and amniotic fluid volume [2,3,14,15].

This study has shown that not only the presence of ketonuria but its severity had a potentially adverse effect on the results of non stress test and the amniotic fluid volume. All of them had an abnormal fetal non stress test in term of spontaneous deceleration in the fetal heart rate [16].

The results of this study in regard to the frequency of having minor levels of ketone bodies in the urine are similar to the results of a study done by Onyeije and Divon, enrolling 3601 patients with post-term pregnancy over a period of 4 years [3].

In regard to the effect of ketonuria on the amniotic fluid volume in term of alteration in the amniotic fluid index, this study had shown that ketonuria is associated with higher frequency of oligohydramnios with a significant statistical association between ketonuria and the presence of oligohydramions.

A study done recentlyby Rhee et al in South Korea (2005) showed that amniotic fluid assessment is a weaker predictor of poor perinatal outcomes than has been classically suggested [17].

On reviewing the results of this study regarding the relationship of various demographic features of the sample included in this study and the severity of ketonuria, one can conclude that the most important factors that potentially enhances the risk of having severe ketonuria is the gestational age. 80% of patients with severe ketonuria and 75% of patients with moderate ketonuria had passed the 41 week of gestation. This finding can explain the longer time of exposure to the phenomenon of accelerated starvation that can be regarded as the main mechanism used to describe the increased risk of ketonuria in post-term pregnancy.

The process of enhanced ketone production as a result of accelerated starvation becomes significant in the latter portion of pregnancy [18,19]. It becomes progressive and more potentially effective in enhancing ketone production from week to week in the later portion of pregnancy and of course it becomes more important in the setting of post-term pregnancy.

In final conclusion one could say that the most powerful factor that can affect the severity of maternal ketonuria is the gestational age, and that ketonuria and its severity had statistically significant association with oligohydramnios and abnormal results of non-stress test, in term of fetal heart rate deceleration or non reactive non stress test.

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Correspondence to Dr. Wafaa S. Abd-Alamieer
E-mail: walhili@yahoo.com
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