Original Article

Comparison of frequency of low APGAR score in babies born to normotensive patients with and without hyperuricemia in a tertiary care hospital

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Abstract

Objective: To compare the frequency of low APGAR scores in babies born to normotensive patients with asymptomatic hyperuricemia with those without hyperuricemia.

Materials and Methods: This cohort study was conducted at the department of gynaecology/obstetrics, Liaquat National Hospital Karachi from January 2015 to January 2016. The sample size was calculated by using openepic.com version 2, an open-source calculator. The sample size was calculated to be 165 in each group, which made a total of 330 patients. Non-probability consecutive sampling was chosen as the sampling technique. All normotensive pregnant females with blood pressure of less than 130/90 between 18 to 40 years of age, with singleton pregnancy at 37 weeks and beyond were included in the study. Normotensive pregnant females with hyperuricemia were the exposed group while normotensive pregnant females with normal uric acid levels were the non-exposed group. The exclusion criteria included patients with multiple gestations, medical disorders like gout, chronic renal failure, APLS, Rheumatoid Arthritis, etc, on anti-hypertensives and smokers. Fetal outcomes were assessed in all patients after delivery and a comparison of outcomes was made between two groups.

Results: The study was designed to compare the frequencies of low APGAR scores in babies born to normotensive patients with asymptomatic hyperuricemia to those without hyperuricemia. The main outcome in group A i.e. exposed group was 29 babies with low APGAR score (<7) with 17.5% and in group B, which was non-exposed, 12 (7.57%) of babies had low APGAR score (<7). P-value came out to be 0.0010. The difference was statistically significant.

Conclusion: It is concluded that there is a significant difference between the frequency of low APGAR scores in babies born to normotensive patients with hyperuricemia to those without hyperuricemia.

Keywords: Hyperuricemia, uric acid, APGAR score.

Introduction

The continuous effort to optimize maternal and fetal health is of crucial importance in leading to extensive research in the field of obstetrics and gynecology. Maternal health during pregnancy is of utmost importance for an acceptable fetal outcome. It is a fact that the majority of maternal and perinatal morbidity and mortality is contributed by pre-eclampsia which complicates around 2 – 8% of pregnancies.[1] Uric acid produced as a final byproduct of purine degradation in the liver by endogenous and exogenous precursor proteins is mainly excreted via kidneys (65%) and intestines (35%). At normal physiologic concentrations, excellent anti-oxidant activity is exhibited by uric acid, but in the case when uric acid exceeds normal levels in plasma, oxidative damage is triggered. A chronic rise in the uric acid level is a significant risk factor for inflammation and dysfunction of endothelial cells.[2,3] The threshold values of 6 mg/dl (530 u /L) and 5.6mg/dl at 38 weeks of pregnancy have been extensively reported in the literature, whereas, a mean uric acid level of 363 umol /L or more is reported[4,5] to be associated with unfavourable outcomes during pregnancy[6]. Recent evidence has reported that hyperuricemia in the fetus itself is associated with infant respiratory distress syndrome.[7] A research estimated that 20% of the general population suffers from asymptomatic hyperuricemia.[8] Though not proven, the circulating uric acid may be directly responsible for the adverse fetal outcome rather than these effects being observed due to pre-eclampsia and other diseases indirectly.[9]

It has been shown that uric acid freely crosses the placenta. It has also been demonstrated that levels of uric acid vary according to gestational age.[10] Serum uric acid estimation has been demonstrated as a marker for preeclampsia in hypertensive pregnancies.[11] It is however not routinely recommended for use in normotensive pregnant patients. A very recent study demonstrated that asymptomatic hyperuricemia in normotensive patients carried a poor fetal outcome as they observed that 17.4% of neonates born to such females had significantly low APGAR scores while only 7.3% of neonates born to females with normal serum uric acid had low APGAR score.[9] This is the only study undertaken previously to the best of our knowledge, but the issue highlighted is a grave one. With a 20% prevalence of asymptomatic hyperuricemia in population[8], it may be the silent morbidity of many babies born with low APGAR score to mothers with no obvious risk factors.

No study has been done in Pakistan till now; therefore this study aimed to assess the findings of this research in Pakistan, both for investigation of this hypothesis and to provide a local context in the matter.

Materials and Methods

The Cohort study was conducted at the obstetrics and gynecology department of Liaquat National Hospital Karachi over a period of one year i.e., from 1st January 2015 to January 2016 after taking permission from the ethical committee of the hospital. The sample size was calculated by using openepi.com version 2, open-source calculation taking the prevalence of low APGAR score in babies of mothers with hyperuricemia to be 17.4% and 7.3% to those babies born to mothers without hyperuricemia. The sample size was calculated to be 165 in each group, which made a total of 330 patients. Non-probability consecutive sampling was chosen as sampling technique Serum uric acid was considered raised in pregnancy based on gestational age i.e., at 37 weeks and 1 day and over more than 5.58 mg/dl. Blood pressure of less than 130/90 mmHg was considered normal. APGAR score was calculated at one and five minutes according to the table given below.

Signs	*0*	*1*	*2*
HR (bpm)	Not present	< 100	>100
RR (bpm)	Not present	Slow, irregular	Good crying
MT	Limp	Some flexion of extremities	Active motion
Response to catheter in nostril	No response	Grimace	Cough or sneeze
Color	Blue, Pale	Body pink extremities blue	Completely pink

**HR=Heart Rate, RR=Respiratory Rate, MT=Muscle Tone*

A score of $\leq$ 7 was considered as a low APGAR score in this study.

All normotensive pregnant females between the ages of 18 and 40 years with singleton pregnancies confirmed by ultrasound at 37 weeks of gestation and beyond confirmed from LMP or in case of not sure of dates from first dating scan were included in the

study. Pregnant females with hyperuricemia were the exposed group (A) and pregnant females with normal uric acid levels were the non-exposed group (B).

The exclusion criteria consisted of twins and higher-order gestation confirmed by ultrasound, patients on antihypertensive drugs, or having blood pressure of more than 130/90mmHg with a history of gout and chronic renal disease. Patients who smoked or have a history of substance abuse and those with autoimmune illness were excluded from enrollment in the study.

After taking informed written consent, the blood sample was drawn and a sample was sent for serum uric acid levels to the laboratory. Upon receiving the results, patients were placed accordingly in either the asymptomatic hyperuricemia group (A) or the normal serum uric acid group (B). Once delivered, the APGAR score of the baby was calculated at one and five minutes. A proforma was used to record the patient's demographic profile i.e., age, gestational age, parity, group of the patients, body mass index, mode of delivery, the value of APGAR score at one minute and five minutes, and an outcome that is APGAR score at 5 minutes, serum uric acid levels. Data were analyzed by using SPSS version 13.0. Mean values and standard deviations were computed for numerical variables like age, parity serum uric acid levels and APGAR score. The outcome was a low APGAR score that was labelled as positive when the score was $\leq$ 7. The frequency of low APGAR score was compared between the two groups and a chi-square test was applied and a P-value of <0.05 was considered significant in this study.

Results

This study compared the frequencies of low APGAR score in babies born to normotensive patients with asymptomatic hyperuricemia to those without hyperuricemia.

A total of 330 patients were enrolled in the study. The age-wise distribution in 18-25 years in group A was 49 (29.69%) and group B was 46 (27.87%). In the age group, 26-30 years 27 patients (16.36%) belonged to group A and 42 (25.45%) patients belonged to group B. in the age group of 31-35 years, 58 (35.15%) were in group B. in 36-40 years age group, 31 (18.78%) patients belonged to group A and 36 (21.81%) patients belonged to group B. Mean and SD for age, parity, BMI, serum uric acid and APGAR score is given in tables below.

152 patients (92.12%) had a normal vaginal delivery and 13(7.87%) had a caesarean section in group A, whereas in group B 159(96.36%) patients had a normal vaginal delivery and 06(3.63%) had a caesarean section. The main outcomes i.e., babies born with low APGAR score in group A were 29(17.5%) and in group B it was 12(7.57%) with a P-value of 0.0010.

Stratification of main outcomes with age, gestational age, parity, and mode of delivery is presented in Tables: 4,5,6, and 7 respectively.

Table 1: Age Distribution n = 330

Age Group	*Group A*	*Group B*
18-25 years	49 (29.69%)	46 (27.37%)
26-30 years	27 (16.36%)	42 (25.45%)
31-35 years	58 (35.15%)	41 (24.84%)
36-40 years	31 (18.78%)	36 (21-81%)
Mean and SD for age	31- $\pm$ 5.7	30 $\pm$ 6.41

Table 2: Mean and SD for Demographic Variables n = 330

Mean and SD	*Group A*	*Group B*
Age	31 $\pm$ 5.7	30 $\pm$ 6.41
Parity	2 $\pm$0.81	2 $\pm$ 0.97
BMI	26 $\pm$ 1.17	26 $\pm$ 1.67
Serum uric acid	6.7 $\pm$ 0.316	5.2 $\pm$ 0.55
APGAR score at 01 minute	9 $\pm$ 1.34	9 $\pm$ 0.99
APGAR score at 05 minute	9 $\pm$ 1.34	9 $\pm$ 0.99
Gestational age	38 $\pm$ 0.93	38 $\pm$ 0.94

Table 3: Frequencies and Percentages for Mode of Delivery n=330

Mode of Delivery	*Groups A*		*Group B*	
	Frequencies	Percentages	Frequencies	Percentages
Normal Vaginal Delivery	152	92.19%	159	96.3%
Caesarean Section	13	7.87%	06	3.6%

Table 4: Comparison of Frequencies and Percentages for Low APGAR Score (Main Outcome) n=330

Low APGAR score the main outcome	*Groups A*		*Group B*	
	Frequencies	Percentages	Frequencies	Percentages
Yes	29	17.57%	12	7.57%
No	136	82.42%	153	42.72%

P-Value = 0.0010

Table 5: Stratification of Mean Outcome with Gestational Age n= 330

Gestational Age	*Main outcome of low APGAR score*	*Group A*	*Group B*	*P-value*
37 weeks	Yes	15	04	0.005
	No	62	72	
>37 weeks	Yes	14	08	0.189
	No	74	78	0.189

Table 6: Stratification of Mean Outcome with mode of delivery n= 330

Mode of delivery	*Main outcome of low APGAR score*	*Group A*	*Group B*	*P-value*
Normal vaginal delivery	Yes	16	06	0.009
	No	136	153	
Caesarean section	Yes	13	06	
	No	0	0	

Discussion

Adverse fetal outcomes are significantly associated with hyperuricemia in pregnancy. Fetal growth is suppressed by a higher uric acid concentration during pre-eclampsia by directly inhibiting amino acid transfer in the placenta.[12] It is known that the production of pro-inflammatory substances and vasoconstrictors is stimulated by uric acid, which lowers nitric oxide production and tends to increase the production of thromboxane in vascular smooth muscle cells.[13] As result hyperuricemia is associated with endothelial dysfunction and raised serum uric acid levels which then precede hypertension. In normotensive pregnant females increased serum uric acid in midgestation is associated with insulin resistance and lower birth weights.[14]

The prevalence of hyperuricemia is reported to be increasing worldwide in recent years. An increase in serum uric acid levels and increased consumption of sugar-sweetened beverages, food rich in purines, and alcohol contribute to a higher prevalence of obesity.[15,16]

Our study is comparable to a study done by Amini E et al[9], where it was observed that 17.4% of neonates born to females with asymptomatic, normotensive hyperuricemia had low APGAR score while only 7.3% of neonates born to females with normal uric acid had APGAR score. This difference was statistically significant. In another study by Chang FM et al[10], maternal and neonatal uric acid levels were measured simultaneously in pregnant women with and without gestational hypertension. There was a high correlation and minimal concentration difference between maternal and neonatal uric acid in either normal or hypertensive women suggesting free transfer of uric acid through the placenta in both directions.

Moreover, not only maternal and neonatal uric acid levels were significantly different among normal and hypertensive females but showed higher levels of serum uric acid in accordance with the severity of preeclampsia.

Both maternal and neonatal uric acid had a negative correlation with birth weight, one minute APGAR score, and five minute APGAR score. It is implied that uric acid levels at parturition might provide a reference index for fetal outcomes in pregnancy with gestational hypertension.

Elevated serum uric acid in pregnant women is associated with small for gestational age due to decreased amino acids uptake by the placenta.[17]

Among normotensive pregnant females, hyperuricemia acts as a risk factor for adverse pregnancy outcomes and subsequent development of neonatal hypoglycemia and IVH.

In one study, neonatal hyperuricemia was linked to infant respiratory distress syndrome and asphyxia.[18]

Maternal factors that lead to increased maternal serum uric acid levels are younger age, primigravidity, increased weight gain, and deranged renal function during pregnancy. These associations have been pointed out by other studies.[19]

Results of this study suggesting a significant association between umbilical, maternal, and neonate uric acid levels are supported by literature demonstrating the free transfer of uric acid through placenta tissue. It is suggested that the etiology of poor

neonatal outcomes might be associated with raised maternal uric acid levels. Neonatal hyperuricemia can only be a reflection of maternal hyperuricemia which triggers an oxidation effect leading to inflammation and dysfunction of endothelial cells.[20,21]

Limitation

Very few studies have been done regarding this topic, so more research needs to be done. Taking this study as a reference point, further multicentered research with a larger sample size is recommended.

Conclusion

There is a statistical difference between the frequency of low APGAR score in babies born to normotensive patients with hyperuricemia to those without hyperuricemia.

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