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The Effect of Gestational Age and Birth Weight on Serum Catalase Level as an Antioxidant Marker in Neonates.

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ABSTRACT

Oxidative stress, the imbalance between the production of free radicals and anti-oxidants, results in irreversible cell damage. Birth implies a strong oxidative stress, for the rapid change from relatively hypoxic intra-uterine to the extra-uterine environment. Newborns are more susceptible to oxidative stress. Such oxidative environment; which increases in premature infants from birth before the 37th week of gestation, appears to involve an immaturity in enzymatic and non-enzymatic antioxidant mechanisms. Catalase which is a common antioxidant enzyme, found nearly in all living organisms that are exposed to oxygen and functions to catalyze the decomposition of hydrogen peroxide to water and oxygen. Estimating the effect of gestational age and birth weight on serum catalase activity level, as an antioxidant marker in neonates. Forty neonates (20 full term "FT: and 20 preterm "PT") classified into 4 groups: group I (n=10, FT-AGA), group II (n=10, FT-SGA), group III (n=10, PT-AGA) and group IV (n=10, PT-SGA). Forty umbilical cord blood samples were collected immediately after birth to assess serum catalase activity level by Spectrophotometric method. Mean serum catalase activity level was statistically significant higher in FT group when compared to PT group. In PT group, there was insignificant positive correlation between serum catalase activity level and gestational age and birth weight. In FT group, there was statistically insignificant positive correlation between serum catalase activity level and gestational age. Serum catalase activity level positively correlated with gestational age and birth weight in neonates. The maturation of antioxidant system increases along with increasing gestational age and birth weight.

Keywords: catalase, antioxidant, neonates, gestational age, birth weight.

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INTRODUCTION

Oxidative stress, which is defined as the imbalance between pro-oxidants and anti-oxidants, can occur due to overproduction of reactive oxygen species (ROS), decrease in antioxidant defenses or a combination of these factors [1]. Such imbalance, which is attributed to the inability of biological antioxidant systems to neutralize these ROS, results in irreversible cell damage. However, oxidative stress can occur early in pregnancy and continue in the postnatal period [1-3].

Pregnancy, usually accompanied by oxidative stress, is characterized by dynamic changes in multiple body systems resulting in increased basal oxygen consumption and in changes in energy substrate use by different organs including the fetoplacental unit. Hence, pregnancy is a condition that favors oxidative stress, mostly because of the mitochondria-rich placenta; that produces (ROS). Hence, the placenta is rich in antioxidant defense elements [5]. It is apparent that the intrauterine period of life is a very important period from a nutritional standpoint. The normal fetal growth is a result of complex interaction among the three components of maternal-placental-fetal unit. Moreover, poor fetal growth may further compromise the development of antioxidant defenses of low birth weight (LBW) babies, predisposing them to higher oxidative stress which, in turn, may partly account for increased morbidity and mortality in these infants [6].

Nutritional status of the mother is the most important maternal factor leading to intrauterine growth retardation [7]. A significant correlation was found between some maternal and cord blood oxidative stress markers, particularly in small for gestational age newborns [8, 9]. Birth weight is one of the most important determinants of perinatal, neonatal and postnatal outcomes. Neonatal weight appeared to be the most important parameters reflecting on the level of oxidative stress. Hence, intrauterine malnutrition is associated with significant oxidative stress in small for gestational age (SGA) neonates born at term to malnourished mothers (10). Moreover, fetal stress induced by maternal undernutrition in pregnancy affects the oxidative status at an early stage of development with a sex-dependent pattern [11].

Labor is a very stressful condition, and a cause of significant oxidative stress to both mother and infant. Birth is, in itself, a hyperoxic challenge. Extra uterine aerobic existence requires efficient cellular electron transport systems to produce energy. In concert with energy-producing oxidative metabolism, biochemical defenses protect against oxidation of cellular constituents by oxygen radicals [12].

Free radicals (FR) are highly reactive chemical molecules containing one or more unpaired electrons. Oxygen-derived free radicals, collectively termed reactive oxygen species (ROS), are normally produced in living organisms. When over produced, they are major mediators of cell and tissue injury. There is a critical balance between free radical generation and antioxidant defenses. Oxidative stress in vivo is a degenerative process due to the over production and propagation of FR reactions; that lead to oxidation of lipids, proteins, polysaccharides and to DNA damage [13].

Free radicals have been implicated in the pathogenesis of a wide spectrum of human diseases. Newborns and particularly preterm infants are at high risk of oxidative stress, due to increased production of free radicals at birth, and incompletely developed antioxidant mechanisms, consequently they are very susceptible to free radical oxidative damage [13, 14]. Premature infants are probably developmentally unprepared for extra uterine life in an oxygen-rich environment and exhibit a unique sensitivity to oxidant injury. Diseases associated with premature infants, including bronchopulmonary dysplasia, periventricular leukomalacia, intraventricular hemorrhage, retinopathy of prematurity, and necrotizing enterocolitis, have been linked to free radical-mediated cell and tissue injury [15, 4, 16].

Anti-oxidant defense is made up of intra-cellular and extra-cellular components. Antioxidants, that are essential in maintaining cellular integrity in normal pregnancy by reducing lipid peroxidation reactions, work synergistically to prevent oxidative damage [17]. Superoxide dismutase (SOD), glutathione peroxidase (GPX) and catalase (CAT), together with glutathione (GSH), form the first-line of defense against reactive oxygen species (ROS) in irradiated tissues [18]. Thus, they protect proteins, enzymes, and cells from destruction by peroxides. Antioxidant defense mechanisms include intracellular and extracellular enzymes (e.g. catalase) [19].

Catalase (an iron containing heme protein) is a common antioxidant enzyme found in nearly all living organisms, and is predominantly located in cellular peroxisomes and its functions include catalyzing the decomposition of hydrogen peroxide to water and oxygen [20, 21]. In addition, catalase has one of the highest turnover rates of all enzymes; one molecule of catalase can convert millions of molecules of hydrogen peroxide to water and oxygen each minute [22, 23]. In fact, fetal level of catalase (CAT) progressively increases during gestation, on the contrary, its level decreases progressively with decreasing birth weight.

So, we aimed in the present study to estimate the effect of gestational age and birth weight on serum catalase activity level as an antioxidant marker in neonates.

SUBJECTS AND METHODS

This study was conducted in Obstetric Department and Neonatal ICU of Maternity Hospital, Ain Shams University.

It included 40 healthy neonates classified into 4 groups:

- Group I (FT-AGA): included 10 full-term neonates (their mean GA ± SD: 39.30 ± 1.16 weeks) appropriate for gestational age (their mean BW ± SD: 3.180 ± 0.31 kg).
- Group II (FT-SGA): included 10 full-term neonates (their mean GA ± SD: 39.10 ± 0.99 weeks) small for gestational age (their mean BW ± SD: 1.935 ± 0.344 kg).
- Group III (PT-AGA): included 10 preterm neonates (their mean GA ± SD: 33.90 ± 1.370 weeks) appropriate for gestational age (their mean BW ± SD: 2.165 ± 0.296 kg).
- Group IV (PT-SGA): included 10 preterm neonates (their mean GA ± SD: 34.70 ± 1.160 weeks) small for gestational age (their mean BW ± SD: 1.435 ± 0.271 kg).

All neonates with known intrauterine infection, major malformation, abnormal fetal monitoring, and evidence of perinatal hypoxia or respiratory distress were excluded from the present study.

After obtaining the approval of the ethical committee at the Pediatrics hospital, Ain Shams University, consents for participation in the study were signed by the parents or caregivers.

Detailed antenatal and perinatal history was taken from the mother or attending family member. Delivery was attended and a thorough clinical examination was performed including, Apgar score determination at one and five minutes**,** and assessment of gestational age using new Ballard score [24].

Anthropometric measurements were taken, according to conventional criteria and measuring procedures [25]. Body weight was measured to the nearest 50 gm using regularly calibrated scale, crown to heal length was obtained in transverse position with avoiding disturbing the neonate during measurements, as well as measuring the occipitofrontal circumference. Weight, length and skull circumference were calculated for age based on growth charts [26].

Full systemic examination, including respiratory, cardiovascular and abdominal examination with a complete neurological examination was carried out.

Sampling

Umbilical cord blood samples were withdrawn from all neonates. Serum levels of catalase were assayed by Spectrophotometer method (27). (Johansson and Borg, 1988). (Cayman Chemical Company, 1180 E. Ellsworth Rd. Ann Arbor, MI 48108 USA). This method utilizes the peroxidation function of Catalase for determination of enzyme activity. It is based on the reaction of the enzyme with methanol in the presence of an optimal concentration of H2O2. The formaldehyde produced is measured calorimetrically with 4-amino-3hydtrazine-5-mercapto-1,2,4-triazole (purpald) as the chromogen. On oxidation this chromogen changes from colorless to purple color.

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Statistical methodology

Statistical presentation and analysis of the present study was conducted, using the mean, standard deviation, t-test, chi-square test and correlations between parameters were calculated by linear regression analysis ROC Curve (receiver operator characteristic curve was used to find out the best cut off value, and validity of certain variable.)

Data were processed with Statistical Package for the Social Sciences (SPSS), Version 16.

RESULTS

Mean serum Catalase activity level was significantly higher in full term group (2.63±0.67nmol/min/ml) compared to preterm group (1.79± 0.64nmol/min/ml**)** (t=4.04) (P<0.0001) (figure 1).No significant difference in mean Serum Catalase activity level between FT-AGA group(2.44±0.57 nmol/min/ml) and FT-SGA group (2.82±0.73 nmol/min/ml)(P>0.05). Also, no significant difference in mean serum Catalase activity level between PT-AGA group (1.79±0.66 nmol/min/ml)and PT-SGA group (1.79±0.66 nmol/min/ml) (P>0.05). Significant higher mean serum Catalase activity level in FT-AGA group compared to PT-AGA group (P<0.05). Also, significant higher mean serum Catalase activity level in FT-SGA group compared to PT-SGA group (P<0.01) (tables 1-5).

There was significant positive correlation between serum catalase activity level in the 40 studied neonates and gestational age; yet, there were no correlation between serum catalase activity level and birth weight, maternal age, length, head circumference and Apgar score at 1 and 5min (table 6).

There was significant negative correlation between serum catalase activity level in full term group and head circumference (figure 2), yet there is insignificant negative correlation between serum catalase activity level and birth weight, length, maternal age, Apgar score at 1min and at 5min.

Also, our study revealed a significant negative correlation between serum catalase activity level in FT-AGA group and Apgar score at 1min was found (figure 3), while, there was no correlation between serum catalase activity level in FT-AGA group and FT-SGA group with different clinical data. No significant correlation was found between serum catalase activity level in preterm group, whether AGA or SGA, and different clinical parameters.

Table 1. Mean serum Catalase activity level in full term and preterm groups.

	Full term group N=20		Preterm group N=20		t	p value	Sig.
	Mean	±SD	Mean	±SD			
Serum Catalase activity level in umbilical cord blood sample (nmol/ min/ml)	2.63	±0.67	1.79	±0.64	4.04	0.0001	**HS**

Table 2. Mean serum Catalase activity level in FT-AGA and FT-SGA groups.

	FT-AGA group N=10		FT-SGA group N=10		t	p value	Sig.
	Mean	±SD	Mean	±SD			
Serum Catalase activity level in umbilical cord blood sample (nmol/min/ml)	2.44	±0.57	2.82	±0.73	-1.28	0.214	NS

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Table 3. Mean serum Catalase activity level in PT-AGA and PT-SGA groups.

	PT-AGA group N=10		PT-SGA group N=10		t	p value	Sig.
	Mean	±SD	Mean	±SD			
Serum Catalase activity level in umbilical cord blood sample (nmol/min/ml)	1.79	±0.66	1.79	±0.66	0.00	1.00	NS

Table 4. Mean serum Catalase activity level in FT-AGA and PT-AGA groups.

	FT-AGA group N=10		PT-AGA group N=10		t	p value	Sig.
	Mean	±SD	Mean	±SD			
Serum Catalase activity level in umbilical cord blood sample (nmol/min/ml)	2.44	±0.57	1.79	±0.66	2.359	0.030	S

Table 5. Mean serum Catalase activity level in FT-SGA and PT-SGA groups .

	FT-SGA group N=10		PT-SGA group N=10		t	p value	Sig.
	Mean	±SD	Mean	±SD			
Serum Catalase activity level in umbilical cord blood sample (nmol/min/ml)	2.82	±0.73	1.79	±0.66	3.29	0.004	HS

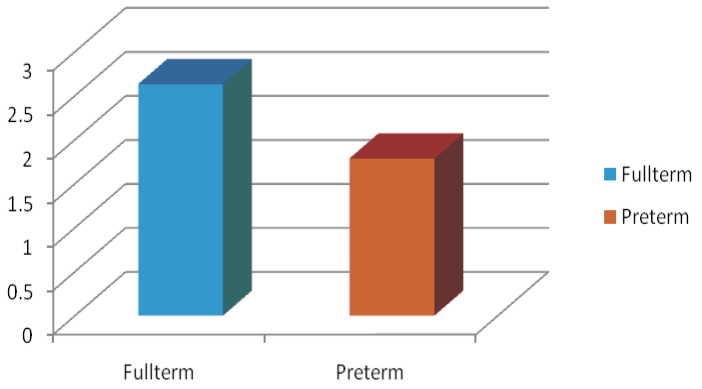

Fig 1: Mean serum Catalase activity level in full term group and preterm group.

Table 6: Correlation between serum catalase activity level and gestational age, birth weight, length, head circumference, maternal age, Apgar score at 1min and at 5min in the 40 studied neonates.

	Serum catalase activity level in umbilical cord blood sample in the 40 studied neonates (nmol/min/ml)		
	R	P value	Sig.
Gestational Age (weeks)	0.577	0.0001	HS
Birth Weight (kg)	0.252	0.117	NS
Length (cm)	0.192	0.236	NS
Head Circumference (cm)	0.301	0.059	NS
Maternal age (years)	-0.108	0.507	NS
Apgar score at 1 min	-0.057	0.728	NS
Apgar score at 5 min	0.084	0.605	NS

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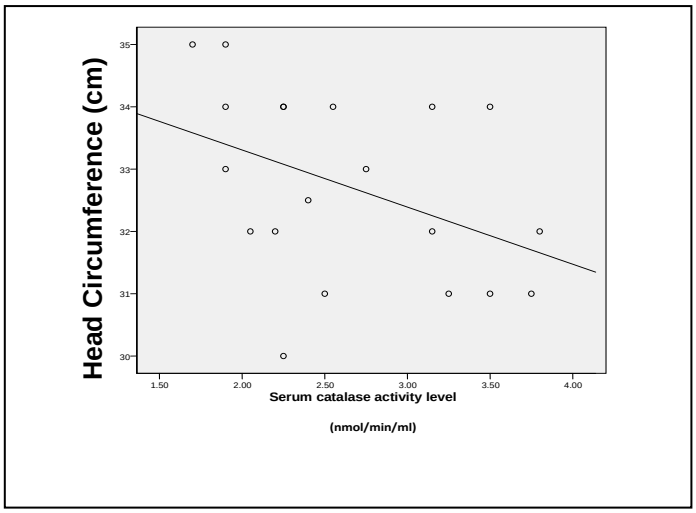

Fig. 2. **Correlation between serum catalase activity level in full term group and head circumference. (r = -0.455, P<0.05 = Significant)**

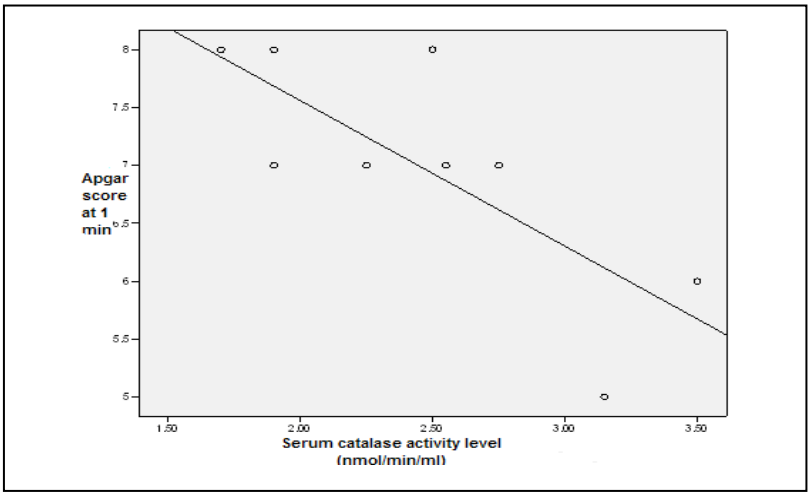

Fig. 3. **Correlation between serum catalase activity level in FT-AGA group and Apgar score at 1min.(r = -0.763, P<0.05 = Significant**

DISCUSSION

Fetal growth is a complex process involving the interaction of mother, placenta and fetus. In recent years, the role of decreasing antioxidants and increasing superoxides is gaining importance as they are threat for the normal pregnancy. Pringsheim et al [28] proved that the intrauterine environment affects the health of an individual not only in fetal life, but also throughout postnatal life. Although, there are still some knowledge gaps regarding oxidative stress during pregnancy and their reflection on neonates [29].

Neonates, particularly preterm and low-birth weight infants, are at high risk of oxidative stress and they are very susceptible to free radical oxidative damage [13, 30]. Birth is, in itself, a hyperoxic challenge. Extra uterine aerobic existence requires efficient cellular electron transport systems to produce energy. In concert with energy-producing oxidative metabolism, biochemical defenses protect against oxidation of cellular constituents by oxygen radicals [12]. Birth weight is one of the most important determinants of perinatal, neonatal and postnatal outcomes [28]. *Saker et al.* (31) and *Al-Gubory et al* [32] concluded that maternal or fetal oxidative stress plays an important role in the pathophysiology of low birth weight. Moreover, *Malti-Boudilmi et al*. [8] concluded that there were significant relationships between maternal and neonate oxidative stress biomarkers.

Anuradha et al [33] concluded that as maternal catalase enzyme increases, babies' birth weight increases. Also, *Bilakhia et al* [30] stated that Catalase level correlates positively with increasing fetal weight. In the present study, the mean serum catalase activity level was found to be significantly higher in the full term (FT) group when compared to the preterm (PT) group. This comes in agreement with the results of *Varga et al.* [34] who demonstrated that the difference between the activity of RBC catalase of premature and full-term neonates was found to be significant. They explained the lower antioxidant enzymatic activity in premature infants by the immaturity of the biochemical systems and the different lipid composition of the RBC membranes. *Georgeson et al* [35] found that CAT activity was significantly higher in full-term than in preterm newborns. Also, *Georgeson et al.* [35] and *Litvinenko et al.* [36] observed low activity of blood catalase in premature babies. Yet *Ochoa et al.* [37] stated that catalase activity was similar between preterm neonates compared to full terms.

In the current study, the mean serum catalase activity level was found to be higher in FT-SGA group when compared to FT-AGA group but the difference was statistically insignificant. When comparing the mean serum catalase activity level between PT-AGA group and PT-SGA group in the present study, it was found that there is no significant difference between both groups. Similarly, *Lee and Chou* [12] reported that FT-SGA infants had statistically significant higher catalase activity level than the FT-AGA infants. They also found that LPT infants had lower levels of CAT activity than the FT-AGA infants. Also, SPT infants showed the same pattern of differences in various antioxidants as those of the LPT infants when compared to FT-AGA infants. They concluded that intrauterine growth retardation and prematurity may influence antioxidant imbalance and free radical damage. In addition, such data for healthy full term and preterm infants may be used as reference data when evaluating antioxidant deficiency in high-risk neonates. On the contrary, *Saker et al.* [31] found that catalase activities were significantly lower in FT-SGA newborns than those of FT-AGA controls.

Gupta et al [10] found that the activity of catalase was significantly lower in term SGA newborns; born to undernourished mothers as compared to term AGA newborns; born to healthy mothers. These studies prove that there is a strong evidence of oxidative stress in the SGA babies born to undernourished mothers, thus indicating that intrauterine malnutrition is associated with significant oxidative stress in SGA term neonates born to malnourished mothers. Their data revealed that the total antioxidant activity was decreased reflecting oxidative stress in SGA newborns and in their mothers. In addition, plasma hydroperoxide and carbonyl protein levels were increased in SGA groups. Their data suggested that intrauterine restriction is associated with significant oxidative stress in SGA newborns and in their mothers. Such studies provide a unique opportunity to have an insight into the mechanism and implications of the fetal growth retardation, secondary to intrauterine malnutrition.

In addition, *Hracsko et al.* [38] demonstrated that full terms with intrauterine growth retardation had lower catalase activities when compared to FT-AGA control group and the difference was statistically highly significant. Also *Kumar et al.* [6] demonstrated that levels of catalase were significantly lower in LBW newborns compared to controls, with the lowest levels found in newborns showing more severe growth restriction (<2000 g), and concluded that LBW newborns are deficient in several important antioxidants which may predispose them to higher oxidative stress, which might have significant implications, as diseases like infection and perinatal asphyxia are much more common in this group.

In our study mean serum catalase activity level was statistically significant higher in FT-AGA group when compared to PT-AGA group. We also found that mean serum catalase activity level was higher in FT-SGA group when compared to PT-SGA group, and there was highly statistical significant difference between the two groups.

Lee and Chou [12], reported that a significant difference in catalase was only observed between small preterms (<33 weeks) and FT-AGA infants, and was not seen between large preterms (33-36 weeks) and FT-AGA infants. They stated that the inadequate difference in gestational ages among the FT-AGA, FT-SGA and Large preterm infants may have contributed to these results.

In the current study, a highly significant positive correlation was found between serum catalase activity level and gestational age in the 40 studied neonates, this comes in agreement with the studies done by *Candlish et al.* [39], *Hayashibe et al.* [40], *Gerdin et al.* [41], *Varga et al.* [42] and *Frank and Groseclose* [23] who showed that catalase activity increase along with gestation in many species, especially those born before

the two-thirds point of gestation. They explained this by the immaturity of the biochemical systems and the different lipid composition of the RBC membranes. In fact, fetal levels of antioxidant enzymes (AOEs) as catalase (CAT) progressively increases during gestation [43]. Jauniaux et al. [44] concluded that catalase activity was correlated with gestational age, but in this case activity rose steadily and then plateaued at 12 weeks.

Moreover, in the present study, serum catalase activity level in the 40 studied neonates was positively correlated with birth weight, length, head circumference and Apgar score at 5min, yet this correlation was of no statistical significance. While there was insignificant negative correlation between serum catalase activity level and maternal age and Apgar score at 1min. Similarly, *Kumar et al.* [6] demonstrated that serum catalase activity level decreased progressively with decreasing birth weight. This is because newborns suffer incompletely developed antioxidant mechanisms. Poor fetal growth may further compromise the development of antioxidant defenses of low birth weight babies, predisposing them to higher oxidative stress which, in turn, may partly account for increased morbidity and mortality in these infants.

In the present study there was a significant negative correlation between serum catalase activity level and head circumference in the Full term group. Yet, there was insignificant negative correlation between serum catalase activity level in full term group and birth weight, length, maternal age, Apgar score at 1min and at 5min, while there was a non significant positive correlation with gestational age. Meanwhile, *Gupta et al.* [10] concluded that serum catalase activity correlated positively with all the neonatal parameters (e.g. birth weight, length and head circumference), as well as the maternal ones.

Regarding FT-AGA group serum catalase activity level was found to be significantly negatively correlated with Apgar score at 1min, and non significantly negatively correlated with birth weight, head circumference and Apgar score at 5min, while it was non significantly positively correlated with gestational age, length and maternal age. In the present study there was a non significant negative correlation between serum catalase activity level in FT-SGA group and length, head circumference, maternal age and Apgar score at 1min while there was a non significant positive correlation with gestational age, birth weight and Apgar score at 5min.

This study revealed that there was insignificant negative correlation between serum catalase activity level in preterm group and Apgar score at 1min and Apgar score at 5min. While, there was insignificant positive correlation between serum catalase activity level in preterm group and gestational age, birth weight, length, head circumference and maternal age. In the study done by *Lee and Chou* [12], the mean serum catalase activity level was found to be lower in small preterms (<33 weeks) when compared to large preterms (33-36 weeks), but the difference between the two groups was of no statistical significance.

On correlating serum catalase activity level in PT-AGA group with gestational age, length, Apgar score at 1min and Apgar score at 5min, there was insignificant negative correlation, while insignificant positive correlation with birth weight, head circumference and maternal age. The current study revealed a highly significant positive correlation between serum catalase activity level, in PT-SGA group, and gestational age, but insignificant positive correlation with birth weight, length and head circumference. On the contrary, there was insignificant negative correlation between serum catalase activity level, in PT-SGA group, and maternal age and Apgar score at 1min and Apgar score at 5min.

CONCLUSION

Serum catalase activity level positively correlated with gestational age and birth weight in neonates. The maturation of antioxidant system increases along with increasing gestational age and birth weight.

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