# The influence of cord blood renalase and advanced oxidation protein products (AOPPs) on perinatal and anthropometric parameters of newborns of mothers with gestational hypertension

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## Abstract

**Background.** Renalase is an enzyme secreted by the kidneys, which takes part in the regulation of arterial pressure, myocardial contractility and modulation of vascular resistance, but its effect on renalase levels in newborns has not been studied yet. The levels of advanced oxidation protein products (AOPPs) were also evaluated as a marker of oxidative stress.

**Objectives.** This study examined whether renalase and AOPP levels are different in the cord blood of newborns exposed to gestational hypertension (HT). The association of both factors with perinatal and anthropometric data among the studied patients was assessed.

**Materials and methods.** The study included 89 newborns: 30 newborns from the study group, whose mothers were diagnosed with gestational HT, and 59 newborns born from normal pregnancies, who formed the control group. Anthropometric measurements and perinatal data in newborns in both groups were recorded.

**Results.** A significantly lower ($p < 0.001$) concentration of renalase was found in the study group (median (Q1–Q3): 23.96 μg/mL (20.63–26.91 μg/mL)) as compared to the control group (median (Q1–Q3): 37.54 μg/mL (33.78–40.02 μg/mL)). In case of AOPPs, a significantly higher ($p < 0.001$) concentration of AOPPs was observed in the study group (median (Q1–Q3): 131.65 μmol/L (113.80–146.10 μmol/L)) than in the controls (median (Q1–Q3): 93.70 μmol/L (87.10–111.20 μmol/L)).

**Conclusions.** A significant difference between renalase and AOPP concentrations between the study and control groups has been demonstrated. Both factors may influence anthropometric and perinatal outcomes of newborns.

**Key words:** cord blood, gestational hypertension, newborns, renalase, oxidative stress

# Background

Pregnancy is associated with many physiological hemodynamic changes; however, hypertensive disorders of pregnancy (HDP) affect as much as 6–10% of pregnant women in Europe and the USA. Gestational hypertension is a condition characterized by newly diagnosed hypertension (HT) after 20 weeks of pregnancy, without accompanying proteinuria or other biochemical or hematological disturbances. Gestational HT can lead to the development of more complex HDP, such as preeclampsia or eclampsia, which, in addition to HT, are characterized by proteinuria and/or maternal kidney and liver injury, neurological symptoms, hemolysis or thrombocytopenia, and often serious complications in the newborn.[1,2]

Complications of gestational HT are currently considered to be one of the most common causes of maternal death. The life and health of newborns is also endangered due to the increased risk of intrauterine growth retardation or placental abruption, which may result in premature birth and other serious complications requiring hospitalization in the neonatal intensive care unit (NICU). In addition, the risk of an urgent cesarean section is increased, which threatens both mother and child.[3]

Renalase is a recently described flavoprotein oxidase, which takes part in the regulation of the cardiovascular system.[4,5] Numerous clinical studies have proven a significant impact of renalase on heart rate, myocardial contractility and vascular tone. Regardless of its function as an inducer of catecholamine degradation, renalase also has the properties of cytokine: it causes cytoprotective and anti-inflammatory effects, and inhibits cell hypoxia and apoptosis.[6,7] Genetic investigations have revealed the occurrence of single nucleotide polymorphisms (SNPs) in the renalase gene and the association of some of them with selected cardiovascular diseases, kidney diseases, type 1 diabetes, ischemic stroke, female infertility schizophrenia, as well as gestational HT and preeclampsia.[8–12] Renalase is secreted into the blood mainly by the kidneys, but its expression has also been shown in many other organs and tissues such as heart, skeletal muscles, endothelium, small intestine, adipose tissue, brain, liver, as well as in the reproductive/steroidogenic system, which is an interesting finding in the context of this study.[13,14]

Oxidative stress takes part in the development of numerous pathologic conditions and by affecting the prenatal life it may have a deleterious effect by causing perinatal disorders and subsequent neonatal diseases. The oxidative stress is defined as an imbalance between oxidants and antioxidants, which results in the formation of reactive oxygen species (ROS) that react mainly with proteins but also with DNA, nucleotides, lipids, carbohydrates, and cell membrane structure elements. The result of these reactions is a destruction of tissue in the mechanism of hypoxia, hyperoxia, ischemia, and local inflammation.[15,16] Pregnancy-induced HT is a condition of increased risk of exposure to oxidative stress, which can affect both the mother and the child.[17,18]

Advanced oxidation protein products (AOPPs) are albumins whose structure has been modified under oxidative stress generated by ROS, and as a result of these changes in their structure, their antioxidant properties are significantly reduced. Due to their characteristics, AOPPs are well-known and easily quantifiable oxidative stress markers, whose high levels have been determined in patients with diabetes mellitus, cardiovascular diseases, HT, and atherosclerosis.[19–21]

# Objectives

In the present study, the umbilical cord blood has been used as a study material due to its good reflection of the neonate condition in the perinatal period and convenient sampling. The study examined how AOPPs and renalase in the umbilical cord blood of newborns of mothers suffering from gestational HT differ from those parameters in neonates who were born from normotensive pregnancies. Both factors were examined because of their possible association with gestational HT the study group. Furthermore, the investigation was extended by analyzing the association between renalase and AOPP level and neonatal anthropometric measurements and demographic data. The aim was to determine whether changes in cord blood renalase and AOPP concentrations induced by HT affect neonatal outcome data.

# Materials and methods

## Study design and participant criteria

The study included 89 newborns divided into 2 groups: the study group (HT group) including 30 newborns from pregnancies complicated by gestational HT, and the control group consisting of 59 newborns from normotensive pregnancies. All newborns were born in the Multi-Specialist Hospital in Gliwice, Poland, between 2018 and 2020. Mothers of patients from the HT group did not suffer from other diseases besides the gestational HT and did not have arterial HT before pregnancy. Gestational HT was diagnosed according to the guidelines of the Polish Society of Gynaecologists and Obstetricians as HT occurring after 20 weeks of pregnancy, when blood pressure values in office measurements are above 140 mm Hg for systolic blood pressure (SBP) and/or higher than 90 mm Hg for diastolic blood pressure (DBP), without accompanying proteinuria or other biochemical and hematological disorders. Patients qualified to the control group came from physiological pregnancies, their mothers did not have any accompanying diseases before and during pregnancy, and their arterial blood pressure values were normal.

## Ethical issues

This study was conducted in full accordance with the Declaration of Helsinki and was approved by the Bioethics

Committee of the Silesian Medical University in Katowice, Poland (resolution No. KNW/022/KB1/109/18). All participating women were familiarized with the method and purpose of research and signed the informed consent to participate.

## Data and sample collection

Medical data concerning both the mother (age, history of pregnancies and deliveries, accompanying diseases), delivery (course of delivery, gestational age, a group B Streptococcus test result, color of waters) and the newborn (Apgar score, sex, birth weight, body length, head circumference, chest circumference) were recorded. Cord blood was collected from the umbilical vein in the 3rd stage of labor, just after the umbilical cord was tightened. Blood was collected into the ethylenediaminetetraacetic acid (EDTA) tubes, samples were centrifuged and then the serum samples were frozen and stored at –80°C.

## Measurements

Renalase and AOPP concentration determinations were performed at the Department of Medical and Molecular Biology (Faculty of Medical Sciences in Zabrze, Medical University of Silesia in Katowice, Poland). The determination of renalase concentrations was performed with the commercially available enzyme-linked immunosorbent assay (ELISA) kit (Cloud-Clone, Katy, USA). The sensitivity of the set was 1.37 ng/mL, intra-serial error was <10% and extra-serial error was <12%. The AOPP concentrations were determined with spectrophotometric method, using commercial test (Immundiagnostik AG, Bensheim, Germany). The sensitivity of the kit was 11 μmol/L, intra-serial error was <5.6% and extra-serial error was <14.3%.

## Statistical analyses

Because the study variables did not meet the assumptions of normal distribution in each group, the data were presented as median with interquartile range (IQR). The distributions were evaluated using the Shapiro–Wilk test, and in all the variables $p < 0.05$ was considered significant. The Mann–Whitney U test was used to compare variables between groups. The Spearman's rank correlation coefficient was used to analyze the relationship between the variables. Rstudio package and Seaborn library for Python language in Jupyter notebook environment were used to perform the analysis (https://seaborn.pydata.org/).

# Results

Perinatal data on neonates obtained in both groups are presented in Table 1. In both groups, males (58.4%) predominated over the females (41.6%). Most of the newborns included in the study were born by vaginal delivery (89.9%), and a smaller part by cesarean section (10.1%). In case of neonates qualified for the study who were born by cesarean section, the operative delivery took place for elective indications (ophthalmological, orthopedic indications). In the whole group of mothers of children included in the study, a similar percentage of nulliparous (49.4%) and multiparous women (50.6%) was observed.

Mothers of children were 20–41 years old, all the infants were eutrophic, rated on the Apgar scale above 8 points due to good condition and born from clear amniotic fluid at the time of delivery (between 37 and 42 weeks of pregnancy). Among the anthropometric factors (Table 2), a statistically significant difference in gestational age,

**Table 1.** Perinatal data of the patients

| Variable | HT group (n = 30) | Control group (n = 59) | Both groups (n = 89) |
|---|---|---|---|
| Gender | | | |
| Female | 13 (43.3%) | 24 (40.7%) | 37 (41.6%) |
| Male | 17 (56.7%) | 35 (59.3%) | 52 (58.4%) |
| Delivery | | | |
| Normal vaginal | 25 (83.3%) | 55 (93.2%) | 80 (89.9%) |
| Cesarean section | 5 (16.7%) | 4 (6.8%) | 9 (10.1%) |
| Parity | | | |
| Nulliparous | 14 (46.7%) | 30 (50.8%) | 44 (49.4%) |
| Multiparous | 16 (53.3%) | 29 (49.2%) | 45 (50.6%) |

HT – hypertension.

**Table 2.** Anthropometric characteristics of the 2 studied groups

| Parameter | HT group (n = 30) | | | Control group (n = 59) | | | p-value* |
|---|---|---|---|---|---|---|---|
| | median | Q1 | Q3 | median | Q1 | Q3 | |
| Age of the mother [years] | 30.0 | 27.0 | 32.0 | 30.0 | 27.0 | 32.0 | 0.213 |
| Gestational age [weeks] | 39.0 | 38.5 | 40.0 | 40.0 | 39.0 | 40.0 | **0.029** |
| Birth weight [g] | 3265.0 | 3290.0 | 3745.0 | 3300.0 | 3090.0 | 3650.0 | 0.284 |
| Body length [cm] | 53.8 | 53.5 | 56.0 | 55.0 | 54.0 | 56.0 | **0.006** |
| Head circumference [cm] | 33.0 | 33.0 | 34.5 | 34.0 | 32.0 | 35.0 | 0.098 |
| Chest circumference [cm] | 32.0 | 32.0 | 35.0 | 33.0 | 32.0 | 34.0 | **0.048** |

*p-values for Mann–Whitney U test. HT – hypertension; Q1 – 1st quartile; Q3 – 3rd quartile. Values in bold are statistically significant.

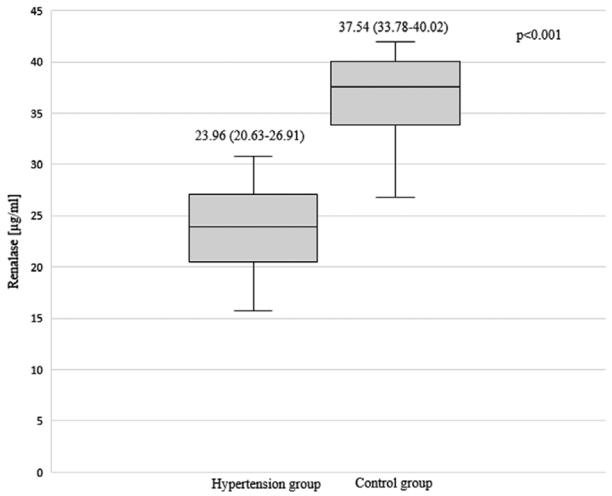


Fig. 1. Renalase concentrations in studied groups. Data are presented as median and interquartile range (IQR). *p-values for Mann–Whitney U test. Z-score value is at 6.787. The graph was prepared without taking outliers into account

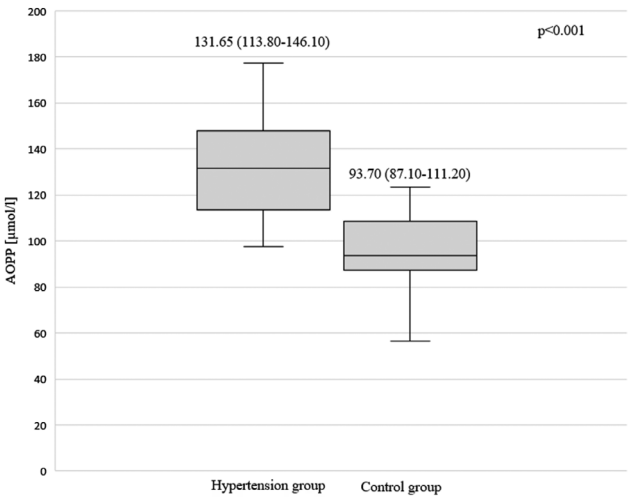


Fig. 2. Advanced oxidation protein product (AOPP) concentrations in studied groups. Data are presented as median and interquartile range (IQR). *p-values for Mann–Whitney U test. Z-score value is at –6.427. The graph was prepared without taking outliers into account

body length and chest circumference was observed: infants in the HT group had a statistically significant lower gestational age, as well as lower body length and chest circumference compared to the control group.

The comparison of renalase and AOPP values in the HT and control groups is presented on a graph and as a median with IQR (Fig. 1,2). A significantly lower ($p < 0.001$) renalase concentration was found in the HT group (23.96 (20.63–26.91) µg/mL) as compared to the control group (37.54 (33.78–40.02) µg/mL). In case of AOPPs, a significantly higher ($p < 0.001$) AOPP concentration was measured in the HT group (131.65 (113.80–146.10) µmol/L) than in the control group (93.70 (87.10–111.20) µmol/L).

In order to establish the association between studied factors and the fetal development, the correlation between the concentrations of the given substances and the demographic, perinatal and anthropometric data of the newborns were analyzed (Table 3). No correlation was found between gestational age and AOPP concentration, as well as between renalase and AOPP concentrations and other studied parameters such as body weight, body length, head circumference, and chest circumference. Renalase and AOPP concentrations were compared in relation to selected perinatal parameters such as gender, type of delivery and parity. A statistically significant difference was found for renalase concentration and parity in the control group, and a significant correlation between AOPP concentration and the type of delivery in the whole population of children included in the study (Table 4,5).

# Discussion

## Renalase

Numerous clinical studies indicate that renalase has a significant effect on the cardiovascular system through its active participation in catecholamine degradation. Probably affecting the reduction of catecholamines in the blood, it directs hemodynamic changes such as a decrease in arterial pressure, myocardial contractility or vascular resistance.[3,5] The pathogenesis of HDP is multifactorial, and one of the most probable theories concerns microcirculation disorders in uterine arteries resulting in impaired

Table 3. Correlation coefficients between anthropometric parameters and renalase and AOPP levels

| Parameter | Renalase | | | | AOPP | | | |
|---|---|---|---|---|---|---|---|---|
| | HT group (n = 30) | p-value | control group (n = 59) | p-value | HT group (n = 30) | p-value | control group (n = 59) | p-value |
| Gestational age | 0.07 | 0.696 | 0.13 | 0.326 | –0.15 | 0.425 | 0.04 | 0.771 |
| Birth weight | –0.16 | 0.392 | 0.06 | 0.657 | 0.04 | 0.846 | 0.13 | 0.329 |
| Birth length | 0.14 | 0.445 | –0.03 | 0.809 | 0.19 | 0.31 | 0.06 | 0.681 |
| Head circumference | –0.06 | 0.773 | –0.01 | 0.913 | –0.07 | 0.717 | 0.10 | 0.457 |
| Chest circumference | –0.13 | 0.509 | –0.01 | 0.919 | –0.09 | 0.652 | 0.09 | 0.492 |

Selected values of Spearman's rank correlation. Statistically significant values ($p < 0.05$) were not observed. HT – hypertension; AOPP – advanced oxidation protein product.

**Table 4.** Renalase concentrations [µg/mL] among neonates exposed to gestational HT in the control group and all neonates included in the study, according to selected perinatal data

| Variable | HT group | Z | p-value* | Control group | Z | p-value* | All neonates | Z | p-value* |
|---|---|---|---|---|---|---|---|---|---|
| Gender | | | | | | | | | |
| Female | 23.0 (21.4–27.9) | −0.02 | 0.982 | 36.4 (33.0–40.0) | −0.71 | 0.477 | 33.3 (27.6–39.4) | −0.4 | 0.690 |
| Male | 24.2 (20.1–26.9) | | | 37.6 (34.5–40.0) | | | 35.5 (26.9–38.3) | | |
| Delivery | | | | | | | | | |
| Normal vaginal | 24.5 (21.0–27.2) | 71.0 | 0.210 | 37.0 (33.8–38.9) | 123.5 | 0.174 | 35.1 (29.0–38.3) | 1.69 | 0.091 |
| Cesarean section | 23.0 (17.6–25.6) | | | 40.1 (32.9–41.8) | | | 26.8 (22.9–40.0) | | |
| Parity | | | | | | | | | |
| Nulliparous | 24.0 (20.1–29.7) | 0.19 | 0.852 | 37.7 (36.5–40.2) | 1.97 | **0.049** | 36.6 (29.0–40.1) | 1.51 | 0.132 |
| Multiparous | 24.0 (20.7–26.6) | | | 35.5 (33.4–38.1) | | | 33.4 (26.2–37.7) | | |

Data are presented as median and interquartile range (IQR). *p-values and Z-score for Mann–Whitney U test; p-values statistically significant (<0.05) are bolded. In subgroups, all the parameters were significantly different between HT group and control group. HT – hypertension.

**Table 5.** Advanced oxidation protein product (AOPP) concentrations [µmol/L] among neonates exposed to gestational HT in the control group and all neonates included in the study, according to selected perinatal data

| Variable | HT group | Z | p-value* | Control group | Z | p-value* | All neonates | Z | p-value* |
|---|---|---|---|---|---|---|---|---|---|
| Gender | | | | | | | | | |
| Female | 131.0 (109.7–142.2) | −0.82 | 0.413 | 94.5 (76.8–112.0) | −0.57 | 0.568 | 105.1 (88.3–121.6) | −0.55 | 0.581 |
| Male | 129.7 (118.5–153.2) | | | 93.7 (88.9–103.2) | | | 102.8 (90.6–122.0) | | |
| Delivery | | | | | | | | | |
| Normal vaginal | 131.1 (111.8–153.3) | −0.33 | 0.741 | 94.1 (86.7–112.0) | −0.32 | 0.752 | 102.7 (88.9–118.9) | −2.05 | **0.041** |
| Cesarean section | 132.5 (121.5–143.8) | | | 93.5 (91.2–104.3) | | | 120.7 (102.3–135.2) | | |
| Parity | | | | | | | | | |
| Nulliparous | 134.4 (118.5–146.1) | 0.17 | 0.868 | 93.5 (88.4–112.8) | 0.16 | 0.874 | 103.7 (89.3–121.7) | −0.07 | 0.944 |
| Multiparous | 128.8 (113.3–147.3) | | | 96.5 (86.2–105.8) | | | 105.8 (87.7–122.5) | | |

Data are presented as median and interquartile range (IQR). *p-values and Z-score for Mann–Whitney U test; p-values statistically significant (<0.05) are bolded. In subgroups, all the parameters were significantly different between HT group and control group. HT – hypertension.

placental blood flow.[22] The evaluation of the effect of renalase on the development of microcirculation in the placenta may give an interesting diagnostic and therapeutic effect. Relationships between renalase and the female reproductive system as well as pregnancy were demonstrated in many fields. Zhou et al. presented results showing high expression of renalase in both male and female gonads, as well as in the renal cortex. Further investigation has shown that the treatment of mice with gonadotropin-releasing hormone (GnRH) antagonist, which reduces the production of steroids, is also associated with reduced expression of renalase in gonads.[15] Clinical trials have also been carried out to link renalase with the occurrence of HDP. The strongest evidence of such connection is proven for rs2576178 and rs10887800 polymorphisms of the renalase genes or their combination. It was also noticed that values of SBP and DBP depend on the genotype dominance.[7–9]

To the best of our knowledge, no studies have been carried out so far to present the evaluation of cord blood renalase concentration among newborns. Publications demonstrating the determinations of serum renalase in pregnant women by Yılmaz et al. and El Niadany et al. reported that the renalase was significantly lower in groups

of pregnant women with HDP compared to the control subjects.[23,24] We observed a similar trend in our study, when lower renalase levels were dectected in the cord blood of neonates exposed to gestational HT than in those from healthy pregnancies.

The observations from the above study provide a clear indication that cord blood renalase concentration is altered as a result of exposure to gestational HT. Considering the knowledge on the various effects of renalase, it seems important to know the exact influence of its concentration fluctuations on neonatal development. To extend the evaluation of the effect of reduced renalase levels on child growth, we correlated renalase concentrations with perinatal and anthropometric parameters of newborns. This analysis has not answered whether anthropometric and perinatal variables are in any way associated with fluctuations in renalase levels.

## Advanced oxidation protein products

Literature data indicate a significant influence of oxidative stress on the development of HDP. Free radicals generate destructive effects on the endothelium of placental blood vessels, and cause increased immunological response, which may lead to the development of HT.[25] The AOPP levels in peripheral blood of pregnant women in various groups of HDP were described as higher than in healthy pregnant women.[18,19] The assessment of the influence of oxidative stress in newborns, especially premature infants, is presented in many studies covering children affected by such conditions as retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), patent ductus arteriosus (PDA), periventricular leukomalacia (PVL), and intraventricular hemorrhage (IVH), together forming a group of free radical-related diseases (FRD). A greater exposure to FRD among premature infants than among children born on their due dates was explained by the fact that the lower the gestational age, the worse the antioxidant response of the fetus. In addition, elevated levels of oxidative stress markers have been proven in newborns exposed to pain.[26–28] Elevated levels of AOPPs and other oxidative stress markers such as ischemia-modified albumin (IMA), thiobarbituric acid reactive substance (TBARS) or serum malondialdehyde (MDA) were detected in peripheral blood of pregnant women with HDP. In addition, it has been observed that in preeclampsia patients, elevated levels of lipid peroxides, which are formed under the influence of ROS, are associated with reduced levels of vitamin E and C, known as first-line antioxidants.[26–28]

Considering the literature data suggesting that oxidative stress occurring in the perinatal period has a significant influence on the development of complications in newborns, we decided to determine the concentration of AOPPs as a well-known marker of oxidative stress in the studied groups. The obtained results clearly show that in the group of neonates born from mothers with gestational HT, the level of AOPPs in cord blood was significantly higher than in the control group. The increased concentration of AOPPs in cord blood in the HT group may provide evidence that exposure to gestational HT induces oxidative stress, which has a direct effect on the child. This conclusion is consistent with observations from other studies stating that the pathogenesis of gestational HT involves the destruction of the endothelium of the placental blood vessels under oxidative stress. Extending the scope of the study to compare anthropometric and perinatal data did not provide a clear answer on the effect of oxidative stress on child development.

## Limitations of the study

Notwithstanding the fact that the results clearly show an association between changes in renalase and AOPP concentrations under the influence of gestational HT, the limitations of our work must be considered. In this study, only neonates born at term and eutrophic were included. The development of gestational HT predisposes to preterm birth and intrauterine hypotrophy, and thus we consider that studies among children with such perinatal complications should be continued. Furthermore, the determination of peripheral blood renalase concentrations in neonates in correlation with blood pressure measurements could explain the process of renalase homeostasis. The relatively small size of the groups was also a limitation of this study, but in the pediatric groups in a single-center research, it is difficult to collect a more numerous study groups.

# Conclusions

A significant difference for both renalase and AOPP concentrations between the study group and the control group has been demonstrated, as well as a correlation of renalase concentration with gestational age. Both factors may influence anthropometric and perinatal outcomes of newborns. Taking into account other literature data on the relaxing effect of renalase on blood vessels, it is likely that renalase disturbances and elevated levels of oxidative stress markers contribute to disorders of placental microcirculation. Further studies aimed at determining renalase and AOPPs in both umbilical and peripheral blood of newborn infants may provide a more complex answer on the causes of HDP and their impact on the development of newborns.

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