**ABSTRACT**

**“Assessment of the endocrine system and biomarkers of metabolism
in patients exposed to prenatal alcohol exposure"**

In term FASD (Fetal Alcohol Spectrum Disorder) covers the existence of physical dysfunctions and disorders in cognitive development, learning and behavior.
FASD is the so-called umbrella of various disorders related to intrauterine exposure
to alcohol. The diagnosis of FASD is the result of the pediatric-neurological-psychiatric
and psychological-developmental diagnosis. There are several diagnostic classifications
in the world to recognize this disease entity.

In 2020, recommendations of Polish experts were issued, in which two diagnostic categories were distinguished: fetal alcohol syndrome (FAS, ICD-10: Q86.0)
and neurodevelopmental disorders related to prenatal alcohol exposure (ND-PAE, ICD-10: G96. 8) and the non-diagnostic category: FASD risk - indicating the need for further observation of the child. The conducted classification is also intended to assess the child's development potential and to determine the scope of the necessary therapeutic support. Among the problems faced by the therapeutic team are also somatic problems, including neurological, metabolic, endocrine, gastrological, rheumatological and immunological problems.

Ethyl alcohol affects the unborn child and causes changes in body structure (specific dysmorphies), malformations of many organs, and above all the central nervous system,
which results in the formation of neurodevelopmental disorders (including emotional development and speech development), psychomotor retardation, intellectual disability, epilepsy, ADHD disorders, autism , difficulties in social relations, a tendency to addiction
to alcohol and other stimulants. Exposure to alcohol also causes developmental changes
in pregnancy and in the postnatal period.

The criteria for diagnosing fully symptomatic Fetal Alcohol Syndrome (FAS) include weight and height deficiency, among others. This deficiency can be described at birth
as small for gestational age (SGA) or at a later stage, and then becomes the focus of attention of pediatric gastrologists and endocrinologists as short stature and weight deficiency in older children. Some patients with short stature can be treated with growth hormone
under the reimbursed drug program after detailed differential diagnosis. Additionally patients with FASD, especially in adolescence, gain excess weight, which is associated
with the appearance of lipid disorders and carbohydrate metabolism disorders.
Due to the chronic exposure to prenatal stress, the hypothalamic-pituitary-adrenal (HPA) axis is also over-activated. Disturbances in steroid production can cause metabolic abnormalities and modulate immune responses (more frequent autoimmune diseases). Research and publications on somatic problems in children with FASD are still limited.

The main goal of this dissertation is to popularize knowledge about children
with FASD and in particular associated endocrine and metabolic disorders, and consequently to improve care for this group of patients, including the spread of the need for multi-profile diagnostics and therapy, taking into account their specific pathologies.

The project was approved by the Bioethics Committee at the University of Rzeszów
on 02/14/2019 (resolution No. 16/02/2019).

The statistical analysis was performed using the Statistica 13.1 PL software
and statistical methods selected for the distribution of variables.

There were 108 children included in the study. After obtaining the consent, the study group consisted of 64 children diagnosed with FASD. All subjects were aged 1-18 years. There were 33 girls and 31 boys in the studied group of patients. The control group consisted of 23 children. Patients were monitored or treated as part of inpatient and outpatient care.
A thorough analysis of the documentation of patients under the care of the author of the study in 2019-2021 was carried out in the field of FASD diagnosis, pregnancy and childbirth interview, anthropometric measurements, parameters of physical development and puberty, as well as laboratory tests, including hormonal, carbohydrate and lipid, calcium
and phosphate metabolism. The following indices of insulin sensitivity and insulin resistance were calculated: IRI / G, HOMA, QUICKI and the atherogenic index (AIP).

The study group was divided into subgroups according to diagnosis
into the following subgroups: FAS, ND-PAE, risk of FASD.

In children with short stature (n = 18), a detailed differential diagnosis was performed
or, due to their young age, they remain in constant outpatient care and their growth velocity
is monitored. Due to the high prevalence of low birth weight (SGA) and intrauterine growth restriction (UIGR), the study group was also divided into subgroups in terms of birth weight.

Due to difficulties experienced by children with FASD (including violence, emotional deprivation, frequent change of guardian, lack of a legal guardian, remaining
in a dysfunctional biological family) very often, e.g. due to the lack of consent, diagnosis and therapy are not possible or are significantly delayed.

In the study group (with present perinatal data), the frequency of SGA was 46.15%
in the FAS group, and 24.24% in the ND-PAE group, which is more than the population frequency. Short stature in the group of children with SGA was found in 35.29% of 20 children with SGA. In the studied group, a strong negative correlation between the SD
of birth weight and the calculated IGF-1 index was demonstrated in the group diagnosed with ND-PAE, as well as a mean correlation in the group of children diagnosed with FAS. Children with SGA may also need to be treated at the endocrinologist's office when they mature and gain weight during puberty. In the study group, 2 girls (1 with FAS
and 1 with ND-PAE) concerned premature puberty. During the observation, early puberty with a poor growth prognosis was also found in 2 girls from the ND-PAE group.
In the studied group, no correlation was found between body weight expressed in the form of standardized body mass index (BMI) and standard deviation of birth weight. Increased cardiovascular risk has been reported in short babies born with low body weight
(small for gestational age, SGA). In the studied population, insulin resistance was found
in 4 children with SGA (20%). In the whole study group, no correlation was found between birth weight and SD of birth weight and standardized metabolic indicators (atherogenic index, insulin / glucose index, HOMA index, QUICKI index, HbA1c). On the other hand,
a positive correlation was demonstrated between the BMI percentile and the HOMA index
in the entire group, and a negative correlation between the BMI percentile and the QIUCKI index in the entire group. However, in the group of children with low birth weight
and diagnosed with FAS and ND-PAE, correlations between the percentile of the BMI body mass index and the insulin resistance indexes (insulin / glucose index and HOMA index) were found. On the other hand, the occurrence of lipid metabolism disorders
was demonstrated. In the entire study group, the presence of hypercholesterolaemia
as well as intermediate and high risk was found, resulting from the calculation of the plasma atherogenic index at the level of 12.69%. When examining the prevalence of lipid metabolism disorders, a greater number of children with hypercholesterolaemia was found in the FAS group (19.23%) compared to the ND-PAE group (6.25%). Similarly, there was
a higher frequency of outcomes indicative of intermediate risk and high atherosclerosis (plasma atherogenic index) in the FAS group compared to ND-PAE. One girl from the RISK FASD group had very low levels of lipid fractions in the serum - the Smith-Lemli-Opitz syndrome was suspected due to the convergent dysmorphology of both syndromes
and referred for further diagnosis to a genetic clinic. Apart from examining dysmorphia, one of the elements of the physical examination of children with FASD is the assessment
of the head circumference. In the studied group, microcephaly affected a significant group of children: 50.91%, including 76.19% in the FAS group, and 40% in the ND-PAE group. The next stage of diagnosis is anthropometric measurements aimed at the occurrence
of growth and nutritional disorders. In the group below the 5th percentile, body mass index was found in 46.15% in the FAS group and in 12.12% in the ND-PAE group. Analyzing
the data by gender, the BMI in the FAS group was 64.28% in girls and 25% in boys,
and in the ND-PAE group in 17.64% in girls and 6.25% in boys. Conducting a combined analysis of body weight and height as well as coexistence of short stature and weight deficiency, the incidence of low body weight and short stature (both parameters <3 percentile) in the whole group was 25.0%, in individual groups N1 - 17.19%: N2 -7.81%, N3 – 0.0%. In the study group, children with FAS had a body height below the 10th percentile in 73.08%, and below the 3rd percentile 53.85%. In the group of children with ND-PAE, body height below the 10th percentile was found in 36.36%, and below the 3rd percentile in 21.21%.
As in the literature, the frequency of short stature increases with the severity of the diagnostic features of FAS. Most of the studies in children with FASD focus on height, but there is little emphasis on the prevalence of overweight and obesity in this population. It is necessary
to prevent excessive weight gain from an early age, also due to special dietary preferences. In the studied group of patients with FASD, 1 case of celiac disease was detected. It coexisted in a girl (with FAS) with somatrotropin hypopituitarism. There was also a correlation between the height percentile and the IGF-1 index in the whole group. Lower IGF-1 values ​​were found in children of lower percentile ranges. These observations are linked
to confirming that decreased IGF-1 levels are associated with low growth and the severity of prenatal alcohol exposure. In the whole study group, a positive correlation was also found between the BMI percentile and IGF-1 index, which is also indicated by the data
from the literature. Similar relationships were shown for the body mass percentiles
and IGF-1 index - higher mass correlated with higher IGF-1. During the evaluation
of hormonal tests, hypothyroidism was diagnosed in the study group in 2 children, including 1 girl treated with growth hormone due to somatotropin-induced pituitary insufficiency. During the observation period, 1 girl had a temporary hyperthyroidism due to Hashimoto's disease. In the whole group, however, there were no disturbances of the HPA axis in the form of increased levels of cortisol and ACTH, and no stress stimuli were used, apart from those related to blood sampling. No disturbances in calcium and phosphate metabolism were found in the study group. However, a significant intensification of vitamin D deficiency was demonstrated in 54.84% of children with SGA selected from the entire study group, which indicates the need to monitor this parameter.

When assessing the dependencies, in the studied group no correlation was found between the percentile of the body mass index (BMI) and the parameters of lipid and carbohydrate metabolism and he concentration of Klotho protein. Higher concentration of Klotho protein were observed in the patient group with FASD and microcephaly compared to the group with normal head circumference, however they were not statistically significant. More research
is needed on the effects of Klotho protein on the cognitive functions of children with FASD.

Based on the analyzes, the following conclusions were drawn:

1. Among children with FASD, a significant percentage are patients with low birth weight, who require systematic observation and prophylaxis due to an increased risk of developing insulin resistance, type 2 diabetes and lipid disorders (especially overweight / obese patients).
2. Due to the significant percentage of children with FASD with insufficient vitamin D level, it is necessary to monitor its level and its proper supplementation, especially
in the group of patients with low birth weight.
3. The population of children with FASD and the risk of FASD, due to the high percentage of short stature and low birth weight, requires monitoring for growth and maturation disorders.
4. In all cases of short stature in FASD and SGA, a detailed differential diagnosis should be performed due to the possibility of rarer causes.
5. Due to the significant percentage of overweight and obesity in pre- and adolescent children, especially in girls, this condition may require targeted intervention
in the prepubertal age.
6. In the analized group of patients higher concentrations of Klotho protein were observed in the group of patients with FASD and microcephaly compared to the group with correct head circumference, the differences were not statisticalily significant. More research is needed on the effect of Klotho protein on the incidence of microcephaly and cognitive impairment in children with FASD.