

Review
According to the rector's order №R-109-135/05.04.2024.
by Prof. Dimitrichka Ducheveva Bliznakova, MD, PhD

Tanya Lyubomirova Zlateva, MD was born on 17.11.1992 in Veliko Tarnovo. In 2011 she graduated from High School for Mathematics and Natural Sciences „Vasil Drumev“ with a profile of Biology and Health Education in her hometown, and in 2017 – from Medical University „Prof. Dr. Paraskev Stoyanov“ – Varna. Zlateva has been actively participating in seminars, trainings and congresses since her student days.

After completing her master's degree, she participated in projects of the Department of Pediatrics:

- Feel4Diabetes (2017 – 2019);
- LENA (2018);
- Project „ Cardiovascular and metabolic risk associated with visceral adipose tissue in patients with long-term type 1 diabetes mellitus“(2019 – 2021);
- Project in Department of Social Medicine and Health Management – DigiCare4You (2022)
- Project for early detection and follow-up of full-term and preterm children, born small for their gestational age (2021 -);

Tanya Zlateva's interests are in the field of emergency pediatrics, pediatric intensive care and neonatology.

Tanya Lyubomirova Zlateva is a member of:

- Bulgarian Medical Association (BMA);
- Bulgarian Pediatrics' Association (BPA)
- Bulgarian Neonatology Association (BNA);
- European Society of Pediatric Endocrinology (ESPE).

Academic development:

After successfully winning competitions in 2019, she was enrolled as a doctoral student at the Department “Pediatrics”, and subsequently as an assistant at the same department.

She speaks fluently English and Russian.

Theme of the dissertation:

“Organization and results from a Programme for early detection and follow-up of children born small for their gestational age”

The dissertation contains 180 pages, 11 tables, 29 figures and 16 appendices. 238 sources are cited, of which 11 are in Cyrillic and 227 are in Latin.

The dissertation was conducted in:

- Department of Pediatrics, Medical University – Varna
- 21 neonatal units in Bulgaria

One of the factors for physical development – growth is an important indicator testifying to children's health. It's deviations engage the attention of pediatric scientists. In recent years, growth hormone treatment has been carried out worldwide in children with growth delay - those with growth hormone deficiency, with proven syndromes and abnormalities, or those who are born small for their gestational age and lack postnatal catch-up growth. The last group of children also determined the direction of the present work given that they have special characteristics – early complications, as well as distant ones, especially in the absence of appropriate behavior in childhood. Early complications include hypoglycemia, hypothermia, death, etc., and late complications include obesity, cardiovascular, early puberty, etc. It is desirable that the diagnosis is made on time, as well as starting treatment with growth hormone. Our country follows these trends, but despite this, children with a still late diagnosis are observed in practice. At the time of writing the dissertation work, only one population-based study on full-term SGA children from single-term pregnancies, carried out by Iotova in 1999, is known to the dissertant. Despite the availability of many data on the prevalence of the condition worldwide, epidemiological data are extremely scarce and difficult to access in our country.

The prerequisites for its implementation are well described in the dissertation work, which include:

- Delayed diagnosis of SGA children in our country;
- The diagnosis of SGA children in our country and globally is still late;
- Lack of current data in our country on the frequency, as well as publications with an estimate of SGA sizes at birth (according to the modern accepted Fenton classification standards);
- Need to prepare neonatologists and pediatricians to evaluate these children;
- Urgent need to reduce age at diagnosis and increase coverage and success rates in the treatment of various diseases;
- Need to prepare neonatologists and pediatricians for timely evaluation for children born with small sizes;
- Need for timely treatment with growth hormone (10% of SGA children, according to literature, do not catch up in their growth), prevention of obesity and treatment at early onset of puberty;
- Sufficiently accumulated data on the beneficial influence of scientific and applied programs on the awareness of society, its target groups and medical specialists.

AIM: The objective is clear, ambitious and is a pilot study for the identification, follow-up and prevention of complications in SGA children in Bulgaria. The dissertation emphasizes the need for a basis for the introduction of the Programme in routine neonatological and pediatric practice in our country.

There are **8 tasks**. They are properly structured.

In addition to the analysis of literature data on the incidence and complications of SGA children, the assessment of the knowledge of practicing neonatologists about the prevalence and complications of SGA children at birth is extremely important. The third task is clear and specific and is related to the development of a Programme for timely detection and follow-up of children born SGA, as well as its implementation in interested neonatal treatment facilities. The Programme contains two stages – first (neonatological) and second (endocrinological). The fourth task is related to the detection of syndromic patients early in maternity wards. The fifth, sixth and seventh tasks include the evaluation of the results of the first stage of the Programme, the evaluation of the potential impact of the Programme on society, the evaluation of favorable and difficult factors. The eighth task is the analysis of the proposed approach for early diagnosis, as well as the coverage of children born SGA in order to avoid early and late complications and related syndromes.

Materials and Methods:

- Search in several medical databases

- Survey method – it involves using two surveys. An author's questionnaire was compiled and conducted through an online platform. It consists of 11 questions, 8 of which have indicated answers. This questionnaire determines the material base of neonatological structures, as well as the knowledge of neonatologists about SGA children.

The second author's survey was conducted after a period of 6 months after the start of the pilot Programme. The aim of the second author's questionnaire (10 questions) is to assess the degree of application (implementation) in the involved neonatal structures. The Monkey Survey platform is used.

- Organizational methods - the pilot Programme was created by the Bulgarian Association of Neonatology and the Varna Society of Pediatric Endocrinology. The idea was presented at a conference on neonatology in Hisarya and active preparations for the creation of the described project followed.

- Clinical methods - each newborn was measured in height and weight in a delivery room, as follows from the birth protocol. Height and weight are measured with appropriate devices. The results obtained were compared against the Fenton curves for the respective sex and gestational age. When counting one or both points below the 10th percentile, the newborn is defined as SGA for height (length), weight, or height and weight at the same time, respectively. Upon reaching the age of 2, each child participating in the Programme is invited to see a pediatric endocrinologist. In the office of the endocrinologist, the entire physical examination is carried out, including up-to-date measurement of height, weight, head and abdomen circumference. Based on the examination and recorded auxological data from the measurements at the GP and/or pediatrician, growth assessment – growth channel, target height, target range is carried out. The target range of normal height deviation for each child is defined as the range ± 9 cm for boys and ± 7.5 cm for girls

(Tanner). The body mass index was calculated using Quetelet's formula and compared with CDC reference data.

- Methods of a scientific-applied nature - The Programme includes a PR specialist to disseminate information about it. It was popularized and coordinated by representatives of the Varna Society of Pediatric Endocrinology and the Bulgarian Association of Neonatology. At the beginning and at the end of the pilot Programme, the expected and detected favorable (facilitators) and unfavorable (barriers) factors that had their impact on the degree of application of the project were analyzed.

- Statistical methods - The analysis of data on the auxological indicators of SGA newborn was carried out through SPSS version 25 software.

Using SPSS, several analyses of the data obtained have been carried out:

- o variational analysis of quantitative data: mean, standard deviation.
- o descriptive analysis of qualitative data: absolute number, relative share
- o comparative analysis using the Fisher t-criteria, with differences with $p < 0.05$ taken as statistically significant.

Participants. The selection of participants has been carried out at several levels.

Criteria for the inclusion of MGV participants:

1st year:

- Birth in one of the neonatal structures that joined the Programme in the period of the first stage of the project (01.04.2021 to 30.03.2022)

- Child born premature by gestational term, with height and/or weight below 10th percentile according to Fenton growth curves

- Born full-term child (38-42 gest.week) calculated by Negele's formula for menstrual age (date of last regular menstruation – 3 months + 7 days), which meets the published criteria regarding birth sizes (Yotova, 2002)

- Written informed consent (IC) obtained from parents

2nd year:

- Lack of catch-up growth up to 24 months of age (height and/or weight < 1.5 SD relative to average parental height)

- Failure to withdraw informed consent

Exclusion criteria:

1st year:

- Planned permanent departure from the country next year

- Detection of severe disabilities already during or immediately after birth
- Refusal to participate (absence of a signed IC)

2nd year:

- Severe debilitating illness
- Non-participation in the first part of the project

Results.

The project begins with an analysis of the literature. Little information was found in Bulgarian literature when searching several databases. Eleven (11) full-text publications by Iotova were discovered, examining the problems of full-term SGA children. She introduced the terms and definition related to SGA sizes at birth and child growth (postnatal catch-up/catch-up) in a cohort longitudinal study of seniors from Varna and the region. Her studies have been found on puberty development, abdominal obesity and related cardio-metabolic and cardio-renal risk factors.

By materially providing neonatal units with height and weight devices, the indicators are standardized. The first poll shows the differences in the definition of SGA children – different criteria are still used – Rautenbach-Hoepffner (1972), Lubchenco (1966), New Ballard Score (1991), Fenton (2013).

In organizing the pilot Programme, leaflets, posters and logos were made with the help of an IT specialist and artist. On the idea of prof. Iotova site and FaceBook page are titled „Small with Big Opportunities (SGA)“. Using the martenichki in the logo – large and small, wide recognition of the Programme is sought. The point of the small and large martenichka is to show that this specific group of „small“ children have great opportunities to catch-up and be indistinguishable from their peers.

At the end of the Programme, 794 SGA newborns were found, representing 3.2% of all newborns for the period in the participating clinics in the country. The distribution by district was also monitored. The IC are signed by 443 families with SGA newborns, which represents more than half of the children found. For the entire period of the Programme, 3 neonatological structures work most actively – Stara Zagora, Sliven, Pleven. On the basis of “the diaries of the two coordinators“ and the survey conducted 6 months after the start of the project, barriers (fear in parents, a lot of clinical work, lack of sufficient perseverance, the COVID-19 pandemic, etc.) and facilitators (close collegial relationships, monthly reminders, media coverage, etc) were derived. Resisting by parents during the second stage of the Programme was also reported. Barriers in the second stage are lack of interest from parents, distance from the nearest children's endocrinologist, lack of sufficient knowledge from the GP about SGA children.

The developed algorithm for tracking SGA children is extremely important, which is extremely facilitated in several steps.

Step 1: Define SGA child versus Fenton curves.

Step 2: Have a conversation with the family about the condition and its possible complications.

Step 3: Monthly monitoring of the child's length and weight in an outpatient setting by a GP or pediatrician (possibly also according to data from measurements in the home by a parent)

Step 4: Examination by pediatric endocrinologist at the age of 2.

Discussion.

Taking into account the obtained results, as well as the search for additional information makes it possible to establish the lack of sufficient literature data on the prevalence of SGA births in our country. The fact is that most publications focus on the early problems of SGA children and especially premature children. At the time of the present work, only one population study by Iotova on SGA children from single pregnancies in Varna is known. She conducts detailed research on the metabolic, puberty, cardiovascular and cardiorenal problems of SGA children. After this in-depth study, Zlateva found no new comprehensive ones describing the variety of problems related to SGA birth.

The uneven distribution of the number of newborns by region is impressive, with more than one neonatal unit participating in several cities - Plovdiv, Sofia and Varna. The highest average number of births per year is observed there. The participation of so many neonatal units speaks of sensitizing neonatologists to the problems of SGA children. The large number of neonatologic structures and the high relative share of newborns in them confirm the population nature of the study.

The prevalence detected by area varies enormously – from 1.3% to 10.9%. In the dissertation work, the data with those from other European and world cohorts are well compared. In the literature, the incidence data range from 2% to 20%. Although the frequency below 2% is extremely scarce in the literature, quite a few publications meeting the requirements have been found. The incidence found for the entire period in Pleven, Stara Zagora and Sliven is closest to the incidence of the condition in most publications.

Conclusion.

The presented results in the present dissertation proved that the pilot Programme has great potential, despite the fact that quite difficult factors have been encountered. Despite the measures taken to raise the awareness of both the public and the medical profession, more efforts are needed in this direction.

It is concluded that when conducting a new similar Programme or continuing the current one, it is considered that the need to collect auxological and passport data of all newborns has been proven. The need to introduce measures at central level has also been demonstrated. Strict and rapid measures are needed to preserve narrow specialists in basic medical facilities with universal accessibility.

One of the most important results of this development is the importance of working with society for a better understanding and adoption of preventive intervention programs of public health importance for the sake of better health of Bulgarian children.

Eight (8) conclusions have been drawn, including:

- Publication analysis that shows insufficient interest in SGA status and lack of sufficient epidemiological data;
- Neonatologists need to familiarize themselves with the modern criteria for defining SGA children, as well as with the prevalence and complications associated with the condition;
- A pilot Programme has been developed for timely detection and follow-up of full-term and premature children born SGA;
- An important conclusion is that not a single child with the syndrome was found in the first stage of the project;
- There are three clinics that actively participate in the Program. It is important to convince the other neonatal clinics and to be motivated to work on this type of program;
- Although there are many complicating factors, relevant results have been obtained that show the need to cover SGA children in order to prevent late complications;

The contributions of the dissertation work „Organization and results of a Programme for early detection and follow-up of children born small for their gestational age“ are clearly and precisely derived. They are of a scientifically applied nature.

It is extremely important that it is a Programme with the first known scientific and applied research to cover the born SGA children, raise awareness of the medical profession, as well as increase public awareness. An easy-to-use protocol has been established and structured to define and track full-term and preterm SGA children. The teamwork of neonatologists and pediatric endocrinologists leads to the creation of a network of these specialists to cover SGA children.

The dissertant has 3 full-text publications and 4 participations in national and international forums that meet the requirements for obtaining a scientific degree „PhD“.

The dissertation work of Tanya Zlateva examines an extremely important and socially significant problem concerning children born small for their gestational age. It is important because the poor assessment of these children and the poor knowledge of the problem leads to late complications - obesity, cardiovascular, metabolic, cardio-renal, etc. This work brings clarity not only among neonatologists, but also reaches out to parents and society as a whole. Reaching the teenage years of children born on their way can pose many risks in terms of behavior and self-esteem, leading to serious even mental manifestations. Provided that there are opportunities to diagnose and treat these children, this is a chance for adolescents and the possibility that they will subsequently create a generation without risk of disease. And as Sigmund Froy said „Everything lies in the childhood years“ - if neonatologists and subsequently pediatric endocrinologists create a lean system and network for tracking these children, the problems in this field of neonatology and pediatrics will be much less. Tanya Zlateva is extremely consistent. Zlateva works with enthusiasm and persistence to complete her dissertation at this stage and prove that the important thing in life is to have a dream. And when the dream becomes a reality - in this case to help children born SGA, this is one of the most valuable things for a young scientist and specialist.

I propose to the respected scientific jury to award the educational degree „PhD“ in scientific specialty „Pediatrics“ to Tanya Lyubomirova Zlateva, MD.

30.04.2024

Prof. Dimitrichka Bliznakova, MD, PhD

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