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(REVIEW ARTICLE)

Proposal to expand the concept of intrauterine growth retardation/restriction and separate five types of IUGR using the "MDN method"

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Abstract

The authors of the study developed a new methodology to examine the physical development of neonates, which simultaneous takes into account the maturity (gestational age), development (weight and length standard positions) and nutritional status (the correlation between weight and length standard positions) of a newborn child. The foundation of this method is a matrix which consists eight horizontal rows of weight standard percentile zones and eight columns made up by the rows of the length standard percentile zones rotated 90 degrees vertically. These form a 64-cell MDN percentile matrix, in which the total data of 1,244,918 Hungarian neonates was added, and the stillbirth + infant mortality (SB+IM) rates of each cell were calculated. Based on the results of this process, five distinctive types of IUGR was identified. Based on the results, five characteristically distinct IUGR types were identified: 1/. weight restricted, 2/. length restricted, 3/. weight and length restricted, 4/. overnourished – length restricted and 5/. undernourished – weight restricted. The various occurrence rates and mortality risks of each IUGR type were also calculated. Using this methodology, the screening processes for IUGR during pregnancy and after delivery were also developed.

Keywords: Intrauterine Growth Restriction; IUGR Types; Stillbirth; Infant Mortality

1 Introduction

Even at the beginning of my career, I wondered how obstetricians and neonatologists around the world only considered neonates born under 2,500 grams of weight as premature. Gestational age didn't even matter. Furthermore, neonates are only considered length restricted if their weight at birth is significantly lower (below the 10th weight percentile) than the average value [1-11]. The degree of risk a neonate faces is also determined based on weight class (>2500g, 2500-1500g, 1500-1000g, 1000g>). These practices all suggest that the knowledge of the weight or weight standard position of a newborn child is enough to assess their viability and physical development. However, relying on a single point of data is not sufficient enough.

Why is it not enough to judge physical development just by knowing body weight or weight development (weight standard position)? Because weight groups are very heterogeneous according to gestational age, body length and nutritional status, and these can also be associated with different health conditions. Not to mention that in the different races of the human race living on Earth, the difference between the average birth weights (considering the extreme average values) can be as much as 1000 g (Papua New Guinea: 2400g, Norway: 3450g). based on their position, to

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estimate the degree of physical development of newborns and the insufficiency of physical development?! "No way." I think it's time to see this and move on.

Therefore, when it comes to neonates, the question arises as to why weight is the only criterion that matters and whether it is acceptable to only rely on a single piece of information to determine physical development. Personally, we disagree.

Following this realization, additional parameters were considered in order to determine the physical development and possible restrictions (IUGR) affecting neonates, even within minutes after birth. Although it was a lengthy process, we believe that a potential solution was found.Materials and Method

2   Materials and method

2.1   The MDN-method, a new, complex methodology to examine neonate physical development

In order to determine the physical development of neonates, a method had to be developed that could be used in the delivery room, even minutes after birth. The following parameters were deemed suitable for this process: gestational age (Maturity), weight and the weight standard position along with length and the length standard position (Development), the correlation between weight and length development known as the nutritional status (Nourishment) as well as the gender of the neonate. The name of the MDN-method is an acronym of these main parameters. Biological gender has to be considered as the average sizes of boys and girls are slightly different and require separate standards for examination.

However, there was still the issue of how to simultaneously take all parameters into consideration and represent those. Moreover, the results had to be presented in mathematical terms. Fortunately, the MDN-method [12-15] was developed to provide answers to these challenges:

2.2   The MDN-percentile matrix, the foundation of the MDN-method

A table (matrix) had to be developed with the eight horizontal lines that are separated by seven known weight standard (W) percentile curves (these include the 3rd, 10th, 25th, 50th, 75th, 90th and 97th percentile values). An additional eight columns containing the length standard value zones (L) rotated by ninety degrees were also required. Overlaying these sixteen zones created an 8x8 grid consisting of 64 cells in total. Each neonate can be categorized by the number of their respective weight standard zone (Zone 1: below the 3rd percentile, Zone 2: 3rd-10th percentile... up to Zone 8: over the 97th percentile) (*Figure 1*).

Figure 1 The weight and longitude zones on the matrix, the names of the cells and the positions of the 4 most extreme developmental states

In order to better identify the results located within the cells of the MDN percentile matrix, a designation was given to each cell. For example, W8L1 means that the cell of the neonate is located in zone 8 of the weight standards (W, over the 97th percentile), and zone 1 of the length standards (L, below the 3rd percentile).

In *Figure 1*, we have colored the most critical cells for physical development: in the yellow cell (W1, L1) there are newborns with the smallest weight and also the smallest length. On the other hand, the red cells (W8, L8) contain the heaviest and longest newborns (giant babies). In the green cell (W1, L8) there are newborns with the smallest weight, but also the largest length (so very thin). The dark blue cell contains the newborns with the heaviest weight, but also the smallest length ("overnourished little dwarf") (W8, L1).

The MDN-matrix also allows for the characterization of the neonate's nutritional status through the nourishment index value, which can be determined using the mathematical formula of **NI = W-L**, with W representing the corresponding weight and L representing the corresponding length standard zone. The value of the nourishment index ranges between -7 and +7. The -7 cell is located in the bottom right corner of the matrix, whereas the +7 cell can be found in the upper left corner of it *(Figure 2.)*

Figure 2 Distribution of newborns according to weight, length development and nutritional status on the MDN-percentile matrix

On the following diagram, I will try to visualize how significant differences can be in the physical development of newborns by taking gestational age, body weight, body length and nutrition into account at the same time *(Figure 3.)*
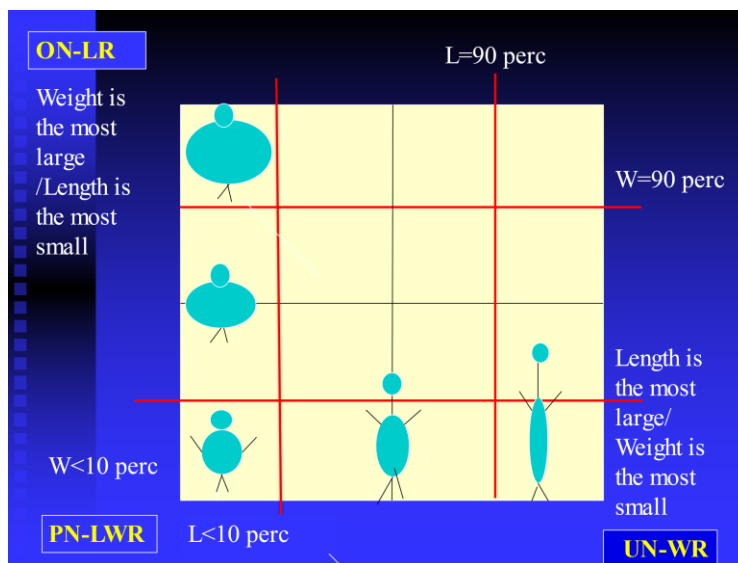

Figure 3 I will try to visualize how significant differences can be in the physical development of newborns by taking gestational age, body weight, body length and nutrition into account at the same time

3 Results

3.1 For us, the most important question was whether physical development affects the risk of stillbirth and infant mortality

According to the Hungarian Central Statistical Office, there were a total of 1,244,918 recorded cases of childbirth in Hungary during the span of 13 years between 2000 and 2012. These included 1,238,891 cases of live births and 6,027 cases of infant mortalities. Using the data from live births, co-author *K. Joubert* created birth weight and length standards for boys and girls respectively [16]. With the use of these percentile standards, the weight and length standard positions of each neonate was determined then added to the 64-cell MDN percentile matrix. Afterwards, the rates of stillbirth, infant mortality, perinatal mortality, late infant mortality and total infant mortality cases were calculated for all possible combinations of weight and length development and nutritional status in each cell.

These calculations revealed how the rate of stillbirth + infant mortality (SB+IM) is affected by weight development (purple numbers and arrow), length development (green numbers and arrow) (*Figure 4)* and nutritional status (*Figure 5)*. The question may arise as to why SB+IM mortality rates were calculated instead of simply adding up the combined rates of stillbirth + infant mortality cases. This decision was made due to a surprising discovery during a later phase of our research: the occurrence rate of IUGR was 40.6% among Hungarian stillbirths and somewhat lower, 29.5% among infant mortality cases. However, the occurrence rate of IUGR among late infant mortality cases was unexpectedly high, 38.0%. The *population average of SB+IM was 10.9‰.*

Figure 4 Stillbirth + Infant Mortality (SB+IM ‰) in the cells and zones of MDN-percentile matrix

As seen on *Figure 4*, the incidence of SB+IM increases with decreasing weight and length.

Figure 5 shows that the risk of mortality is greater if the neonate is undernourished (lacking weight compared to its length) or overnourished (lacking length compared to its weight). Simply put, the risk of mortality increases proportionately with the rate of disharmony between weight and length development.

Figure 5 Stillbiirth + Infant Mortality (SB+IM‰) in the diagonals of newborns with positive and negative nutritional index (NI=W-L)

Overall, it was identified and confirmed that the risk of stillbirth + infant mortality increases if neonates have lower weight and or length values than what is considered standard for the gestational age, or if there is disharmony between length and weight development.

Based on these discoveries, we recommend that the concept and definition of growth restriction should be modified and expanded [17-18].

We believe this is necessary because the increased risk of stillbirth and infant mortality cannot be solely attributed to weight development disorders (a lack of development, impairment, restriction).

3.2   How many types of IUGR can be identified on the MDN percentile matrix?

Next, we examined how many distinctive types of intrauterine growth restriction (IUGR) can be identified and separated on the MDN percentile matrix.

To date, we have only separated the "proportional and disproportionate" IUGR phenotypes below the 10th weight percentile. Given the SB+IM mortality values, we suggest that in the future 5 characteristically different IUGR phenotypes should be separated (Figure 6.) [17-18].

We determined the average SB+IM mortality rate of each type of IUGR in the Hungarian population (per thousandths). In the middle, white square of the MDP-percentile matrix, there are the death results of moderately developed newborns according to their weight and length development (Figure 6).

At the time of writing, distinction is only made between proportionate and disproportionate IUGR phenotypes below the 10th weight percentile. We recommend the use of five distinct types of IUGR in the future (*Figure 6*) [17-18]. The average SB+IM mortality rates of each IUGR type within the Hungarian population were also determined. The results are shown in *Figure 6*:
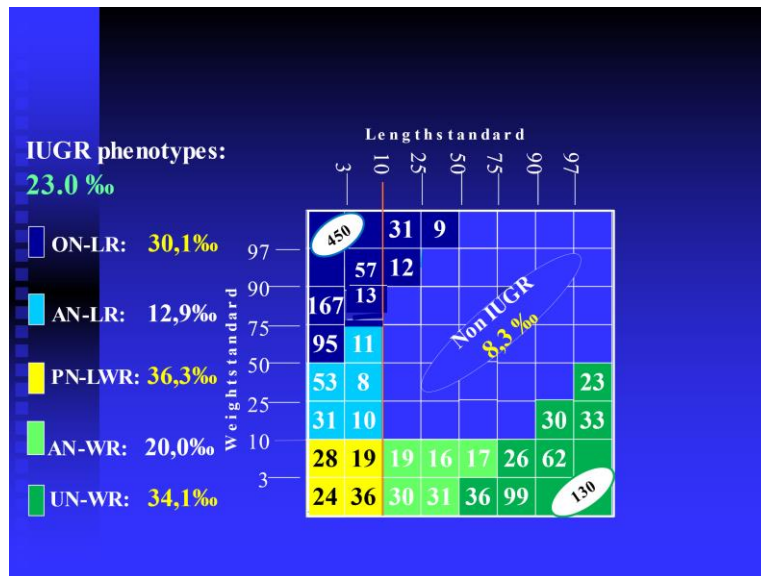
Figure 6 I suggest the definition of IUGR should be expanded and 5 types of IUGR should be distinguished

The names of five separate intrauterine growth restriction types were selected emphasize whether the neonate is underdeveloped in terms of weight, length or nutritional status when compared to averagely developed, 'Non-IUGR' neonates.

- overnourished/length retarded: ON-LR (dark blue cells)
- averagely nourished /length retarded: AN-L R (light blue cells)
- low weight, low length retarded: PN-LWR (yellow cells)
- averagely nourished /weight retarded: AN-W R (light green cells)
- undernourished/ weight retarded: UN WR (dark green cells)

Based on the above, we recommend the expansion of the concept and definiton of intrauterine growth restriction (IUGR) and the adoption of using these five IUGR phenotypes in order to distinguish between IUGR cases.

3.3   What do the Hungarian mortality results show?

The average SB+IM mortality rates of each IUGR type should be compared to the average mortality rate of 'non-IUGR' type fetuses and neonates with average development between the 10th and 90th percentiles (8,1‰, white cells). The cells of IUGR phenotype fetuses and neonates with mortality values that are twice as high or greater than the average rate must be considered as 'high-risk' groups.

Occurrence rates: ON/LR 0.8%, **AN/LR 5.7% - PN/LWR 4.7% - AN/WR 5.5%,** UN/WR 0.7%.

The average SB+IM mortality rates of each IUGR type: ON/LR 30.1‰ - AN/LR 12.9 **‰ - PN/LWR 36.4‰ -** AN/WR 20.0‰ - **UN/WR 34.1‰** *(Figure 6.).* Mortality rate of the averagely developed, Non-IUGR group: 8.1‰

When looking at the SB+IM mortality rates on the MDN percentile matrix, it becomes apparent that certain cells showcase mortality rates that are significantly greater than what is considered average for the specific type of IUGR, particularly in the ON/LR cell group.

It is also apparent, that these extremely high mortality rates can be found in zone 1 of both weight and length standards below the 3rd percentiles and also in cells where the value of the nutritional index is either +5, +6, +7 or -5, -6, -7.

The cells of IUGR phenotype fetuses and neonates with mortality values that are twice as high or greater than the average rate must be considered as *'high-risk'* groups *(Figure 7).*
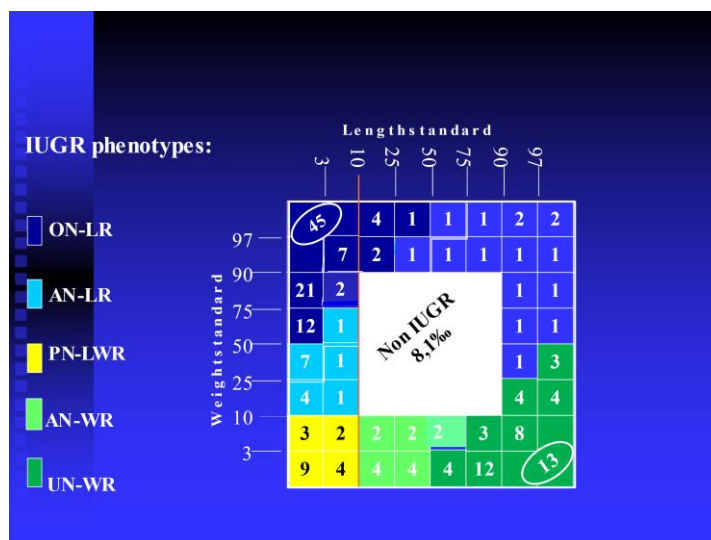
Figure 7 How many times greater is SB+IM death in the cells of the 5 IUGR types than in the Non IUGR group?

4 Discussion

4.1 What can the MDN-method be used for?

- Unlike previously used methodologies, the MDN-method allows for the complex examination and evaluation of neonate physical development based not only on weight, but also on gestational age, weight standard position, length, length standard position, nutritional status and gender.
- The MDN-method allows for the identification and distinction of five base types of developmental disorders and five separate types of intrauterine growth restriction. The risk levels individual IUGR types can also be determined.
- The MDN-method created a basis for the development of a neonate IUGR screening method as well as an IUGR ultrasound screening method for fetuses. These methods allow for the identification of high-risk IUGR phenotype fetuses and neonates.
  The identification of high-risk fetuses and neonates, followed by immediate diagnostic examinations and the appropriate therapeutic measures can save the lives of many fetuses and neonates suffering from IUGR and mitigate the effects of the IUGR condition that only manifest in the later stages of life (during child- and adulthood) [19-20].

4.2 The significance of identifying high-risk IUGR phenotypes

Being categorized as high-risk does not always necessarily mean that all neonates face a greater risk of mortality due to IUGR. It only means that the cell in which a neonate is placed has a higher rate of SB+IM mortality rate than the average mortality rate of non-IUGR neoneates (twice as high as 8.1‰, 16.2 ‰ or greater). The majority of IUGR phenotype neonates placed in IUGR cells are smaller in size due to genetically determined reasons and do no suffer from IUGR.

The sole purpose of IUGR screenings is to determine whether the examined neonate falls into a high-risk cell or not. Additional tests with differential diagnostic accuracy must be performed after screening in order to properly identify whether the neonate suffers from an IUGR condition.

(The process is best comparable to breast cancer screening. Mammography alone does not determine if the patient has breast cancer or not; it is only used to locate lumps that that might be tumours. The lump then has to be punctured and only after the histological examination of the tissue sample can the presence of cancer be confirmed. The IUGR screening of neonates follows the same principle.)

The lives of nearly 300 fetuses and neonates suffering from an IUGR condition could be saved each year in Hungary if IUGR screenings became common and widely used practice. On a global scale, approximately 2-3 million children could be saved annually with the widespread application of the methodology [21].

Ultimately, the MDN-method would serve this noble purpose, if IUGR screening practices were adopted.

Nomenclature

- IUGR – Intrauterine Growth Retardation/Restriction
- MDN – Maturity, Development, Nourishment
- NI – Nutritional Index
- SB+IM – Stillbirth + Infant Mortality
- ON-LR – Overnourished, Length Restricted
- UN-WR –Undernourished, Weight Restricted
- PN-LWR – Proportionally Nourished, Length and Weight Restricted
- AN-LR – Averagely Nourished, Length Restricted
- AN-WR – Averagely Nourished, Weight Restricted

5 Conclusion

The authors have developed a new test method (MDN-method), which allows the physical development of the newborn and the delay in growth (Intrauterine Growth Retardation/Restriction) for 5 parameters (gestational age, body weight, body length, nutritional status and the gender of the newborn) simultaneously taking into account the examination and qualification. Using this method: 1/. There are 5 characteristically different types of IUGR. - 2/. With the help of a software, newborns with an "highly endangered" IUGR phenotype can be screened out in 1 minute. In the case of IUGR newborns screened out in this way, the neonatological differential diagnostic tests can be performed without wasting time, during which it can be decided whether it is a newborn with IUGR who needs treatment, or a newborn who does not need treatment but only has an IUGR phenotype and is smaller due to genetic reasons. If this screening method becomes widespread, the lives of many babies with IUGR can be saved.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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