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Proposal to expand the definition of intrauterine growth restriction and introduce two new screening methods

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Abstract

The authors of this publication have developed a new screening method to evaluate the physical development of infants, which identifies growth and developmental restrictions based on their gestational age, gender, weight and length standard positions and nourishment status. This so-called MDN-method (MDN = Maturity, Development, Nourishment) offers several benefits: 1. It enables the expansion of the scope and definition of intrauterine growth restriction (IUGR) and the establishment of five separate condition subtypes. 2. It facilitates the study of the risk of mortality of infants based on their development and nourishment status. 3. The method is suitable for the screening of high-risk IUGR infants and neonates. 4. The MDN method allowed for the development of a new ultrasound screening methodology for high-risk IUGR infants and neonates, based on abdominal circumference (AC) and femur length (FL) standards, which correlate the most with the weight and length of the fetus. The data of 1,244,918 Hungarian live and stillbirths recorded during 2000-2012 were used for these studies. It is believed that these new screening methods may have a significant impact on reducing the frequency of IUGR-related stillbirth and infant mortality cases.

Keywords: MDN-method; Definition of IUGR; Screening methods of IUGR; Stillbirth; Infant mortality

1. Introduction

We have nothing but respect towards the colleagues who developed the first neonate weight standards and first categorized infants and neonates who were born with lower than average weight as SGA (small for gestational age), dysmature or growth restricted later on. It was also recognized that being underdeveloped in terms of weight significantly increased the risk of infant mortality [1-15]. However, several decades have passed since and we believe that the following questions should be raised in regards to this topic:

- Would it not be more beneficial if the definition of intrauterine growth restriction (IUGR) was not tied to a single weight criteria (IUGR = <10th weight percentile)? What if, in addition to the weight, the gestational age, length, gender and nourishment status of the infant were also considered? After all, this approach is no different from how the physical development of an adult is evaluated, which usually includes the description of height, nourishment and even the estimation of the individual's age, but exact weight is seldom brought up.
- As to why research on growth restriction (IUGR) is so important – Pelleg et al. [16] highlight that IUGR is the primary reason behind stillbirths and the second greatest cause for infant mortality after premature births. Approximately three million fetuses and neonates die each year due to IUGR worldwide.

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- This raises another question: why is the mortality rate of growth restricted fetuses and neonates so high? It can be ruled out that this is due to them lacking in weight or other sizes. Smaller length is only one possible phenotype or consequence of the IUGR condition. Mortality is usually caused by organ failure, which can be attributed to the etiological factors (maternal, placental or fetal) of the IUGR condition. However, in most cases, smaller than average sizes can also be attributed to the genetic makeup of the parents. Not all IUGR phenotype infants suffer from an IUGR condition, but all infants with an IUGR condition are also IUGR phenotypes. Therefore, we believe it is important to differentiate between IUGR phenotypes and the actual IUGR condition.
- It must also be determined whether IUGR affects everyone the same way and if the lack of weight development is truly the sole factor responsible for the higher than average risk of mortality among those affected.

Objective

The aim of the research was to take maturity (gestational age), physical development (weight and length standard positions, based on gender) and nourishment (the relation between weight and length standard positions) parameters all into consideration in order to evaluate overall development. However, this presented several challenges, as there were no methodologies available with which the aforementioned parameters could simultaneously be considered, or to quantify and depict various stages of development.

If the development of a new methodology were to succeed, the development of new intrauterine growth restriction screenings using said methodology would also be possible.

2. Methodology and results

2.1. The MDN method – a new way to examine intrauterine growth restriction (IUGR)

In order to use the MDN method, the gestational age, gender, weight and length of the infant are required, along with gender-specific weight and length standards and a specialized software that calculates the standard positions and the nourishment index of the infant as well [17, 18, 19, 20].

The percentile-scaled standards based on the data of 1,238,891 live-born neonate children in Hungary between 2000 and 2012 (divided into 8 zones by the 3rd, the 10th, the 25th, the 50th, the 75th, the 90th, and the 97th percentiles) developed by *Joubert K, Zsákai A, and Berkő P.* [21-22] are perfectly suitable for this purpose.

2.2. The primary tool of the method, the MDN percentile matrix

Simultaneous depiction of weight and length standard positions is made possible by the MDN percentile matrix developed by *Berkő P and Joubert K*. This matrix consists of 64 cells in an 8×8 grid that resembles a chessboard. Weight standards are represented by 8 horizontal rows (W), numbered 1 to 8, increasing from top to bottom. Length standards, rotated by 90 degrees, are represented by 8 vertical columns (L), increasing from left to right and also numbered. The positions and cells of all possible weight and length combinations can be found on the MDN percentile matrix.

Weight development of the infant is characterized by the number of the corresponding weight standard zone (W) on the MDN percentile matrix. Length development can be determined in a similar manner, using the number of the corresponding length standard zone (L).

2.3. Determining nutritional index

During the compilation of this matrix it was recognized that it is capable of more than just simultaneous depiction of weight and length. The MDN percentile matrix can also display various nutritional states through the depiction of the relations between weight and length. Nutritional status can be characterized numerically by the use of the following formula:

NI (nutritional index) = W-L, with 'W' and 'L' representing the number of the weight/length standard zone of the examined newborn, respectively, based on his or her gestational age and weight/length (zone 1 being the zone under the 3rd percentile and zone 8 being the zone above the 97th percentile). If the NI value is positive (+), there is relative excess weight compared to length of the newborn, meaning the newborn is overnourished. The amount of excess weight increases in line with the NI value. By contrast, if the NI value has a negative sign (-), the newborn is underweight compared to its height and is undernourished.

Figure 1 shows the core component of the MDN method, the MDN percentile matrix. Each cell of the matrix includes its respective nutritional index value. Positive NI values (the rate of overnutrition) increase towards the top left corner of the matrix, whereas negative NI values (the rate of malnutrition) increase towards the bottom right corner of the matrix.

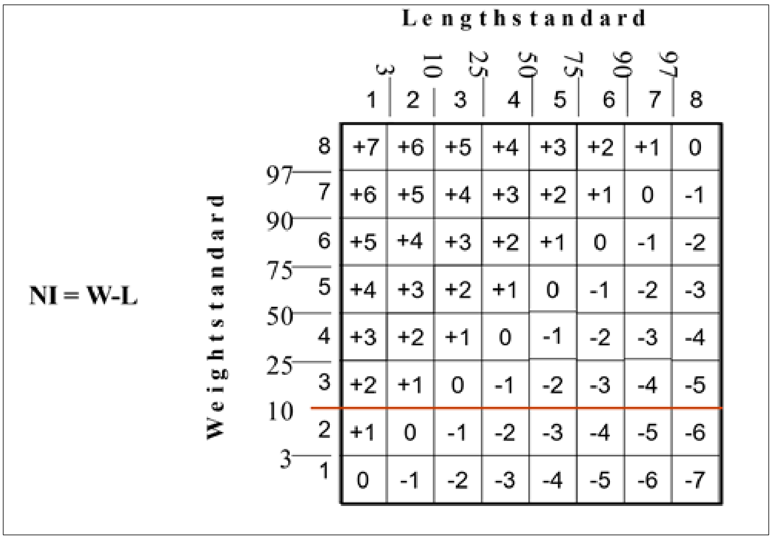

Figure 1 The MDN-percentile matrix, depicting length standard positions (L), weight standard positions (W) and nutritional index (NI=W-L)

Development of the matrix raises the question of whether it can be proven that, in addition to weight, length and nutritional status also have a significant impact on the health of fetuses and neonates.

The cells of the MDN percentile matrix were marked with two-digit numbers for better identification, with the first number representing the weight zone, and the second number representing the length zone of the given infant.

2.4. The benefits of the MDN percentile matrix

The MDN percentile matrix allows the risk of stillbirth and infant mortality to be examined at various stages of physical development. Stillbirth and infant mortality were chosen to be examined over perinatal mortalities because previous studies revealed that IUGR is common among stillbirth (42.3%) and late infant mortality cases (37.4%).

During the examined period of 2000-2012, a total of 1,244,918 live and stillbirths were recorded in Hungary, of which 6027 (44.5%) were stillbirths and 7532 (55.5%) were infant mortality cases. Each of these infants (both live and stillbirths) were added to a single MDN percentile matrix based on their gestational age, gender and sizes (weight and length standard positions).

Figure 2. showcases the results of this process. It was revealed that the highest mortality rates were not exclusive to fetuses and neonates below the 10th weight percentile. The cells of infants and neonates with the shortest length, length restriction (upper left corner), weight restriction (bottom right corner) or length and weight restriction (bottom right corner) also showed high mortality rates. This proves that having lower than average weight (below the 10th percentile) should not be the sole deciding factor in the identification of a high-risk IUGR fetuses and neonates.

	53	15	11	10	9	8	8	8
13	880	333	31	9	9	12	14	13
7	269	57	12	4	5	7	5	3
7	167	13	5	4	8	5	4	5
8	95	11	6	8	10	6	7	12
10	53	8	8	11	9	8	11	23
12	31	10	13	12	10	12	30	33
19	28	19	19	16	17	26	62	19
48	74	36	30	31	36	99	239	250
‰								

Figure 2 Stillbirth + Infant Mortality (SB+IM) (‰) dependent on the weight (W) and length (L) development and the nutritional status (NI) as well

2.5. Proposal to expand the definition of IUGR and establish five separate types of the condition, based on SB+IM results

Based on the SB+IM results of Figure 3, it is apparent that the condition not only affects weight restricted fetuses and neonates but also those with other physical developmental disorders. Therefore the following expansions and modifications to the definition of IUGR are proposed:

IUGR is defined as: (1) the length or weight (or both) of the newborn is significantly below the average size of the given gestational age (below the standard 10th percentile of birth); - (2) a significant disharmony can be observed between weight and height, whether infants are significantly lacking in length compared to their large weight (visibly overnourished, NI = +4, +5, +6, +7) or lacking in weight compared to their weight (visibly underfed, malnourished, NI = -4, -5, -6, -7); (3) any combination of the aforementioned conditions (mixed types).

2.6. The 5 proposed types of IUGR (Figure 3)

2.6.1. Mixed types

Overnourished - Length Retarded (ON-LR)

Infants lacking in length compared to their weight (appearing overnourished), the majority also being retarded in terms of length. Nutritional Index value: +4, +5, +6 or +7. Proportion of ON-LR within the Hungarian newborn population: 0.8%.

Undernourished - Weight Retarded (UN-WR)

Infants lacking in weight compared to their length (appearing undernourished), the majority being retarded in terms of weight. Nutritional Index value: -4, -5, -6 or -7. Proportion of UN-WR within the Hungarian newborn population: 0.7%.

Proportionate Nourished - Length and Weight Retarded (PN-LWR).

Infants with height and weight both below the 10th percentile. Proportion of PN-LWR within the Hungarian newborn population: 4.7%.

2.6.2. Homogenous types

Averagely Nourished - Length Retarded (AN-LR)

Situated between ON-LR and PN-LWR groups, with length below the 10th percentile. Proportion of AN-LR within the Hungarian newborn population: 5.7%.

Averagely Nourished - Weight Retarded (AN-WR)

Situated between PN-LWR and UN-WR groups, with weight below the 10th percentile. Proportion of AN-WR within the Hungarian newborn population: 5.5%.

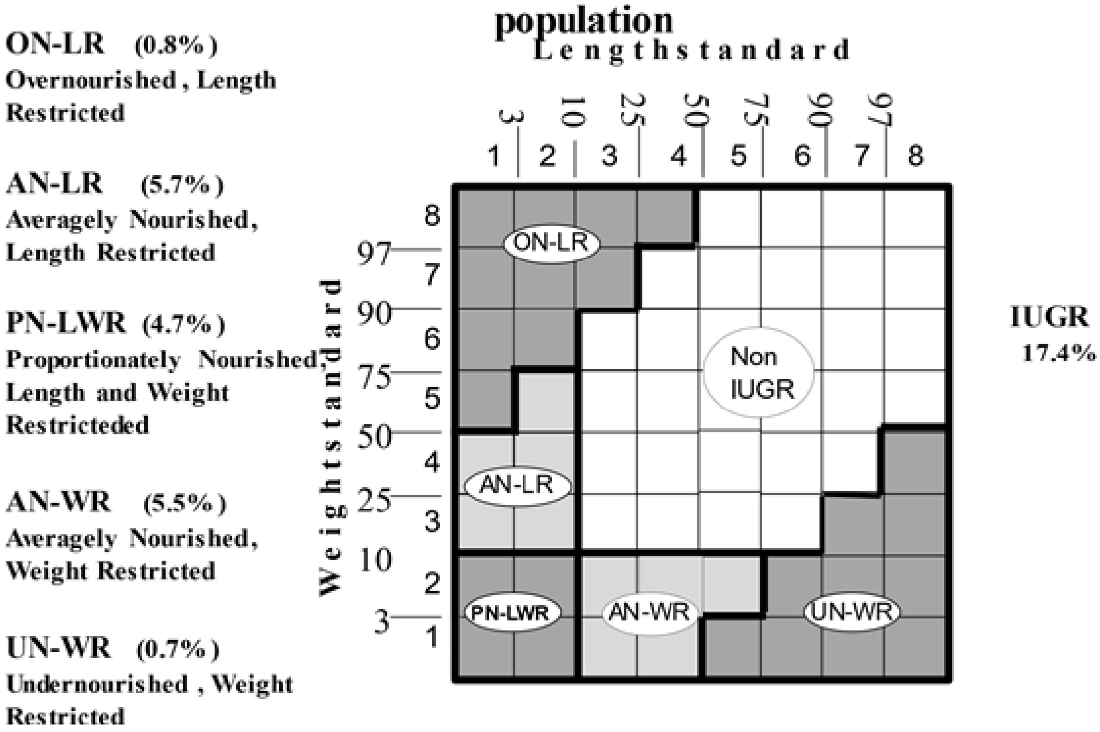

Figure 3 Positions of the five IUGR-phenotypes on the MDN-percentile matrix and their proportions within the total Hungarian neonate population (2000-2012)

2.7. Which types of IUGR have the highest mortality rates?

The stillbirth + infant mortality (SB+IM) rates were included for each cell of the MDN percentile matrix on Figure 5, which presents the following information: 1. The SB+IM rates of the large white sector of non-IUGR phenotypes is 8.3‰. 2. Out of all IUGR types, proportionately nourished, length and weight restricted fetuses and neonates below the 10th percentile have the highest number of SB+IM cases (36.4‰), followed by the undernourished, weight restricted group. Averagely nourished, length restricted types had the lowest number of mortality cases (12.9‰), followed by the averagely nourished, weight restricted group (20.0‰).

2.8. Which infants and neonates are considered 'High-Risk Restricted' (HR-IUGR)?

Fetuses and neonates are considered 'high-risk IUGR' types if the SB+IM value of their respective cells is at least twice as high as that of the 'non-IUGR' group (8.3‰). These cells were highlighted in grey. The SB+IM value of the high-risk IUGR group is over three times greater (28.7‰) than the non-IUGR group's (8.3‰). In the case of certain grey cells, the mortality rate is even higher (*Figure 4.*) [23, 24].

The question arises whether all high-risk neonates suffer from IUGR. Naturally, that is not the case. It is important to emphasize that the majority of IUGR-phenotype neonates do not suffer from an IUGR condition and are merely smaller due to their genetic makeup. Specialized IUGR screenings are necessary in order to determine whether the small size of the infant is due to their genetic background (IUGR-phenotype) or because of an IUGR condition. In the latter case additional differential diagnostic examinations and immediate therapy should be carried out, due to the risks associated to the condition.

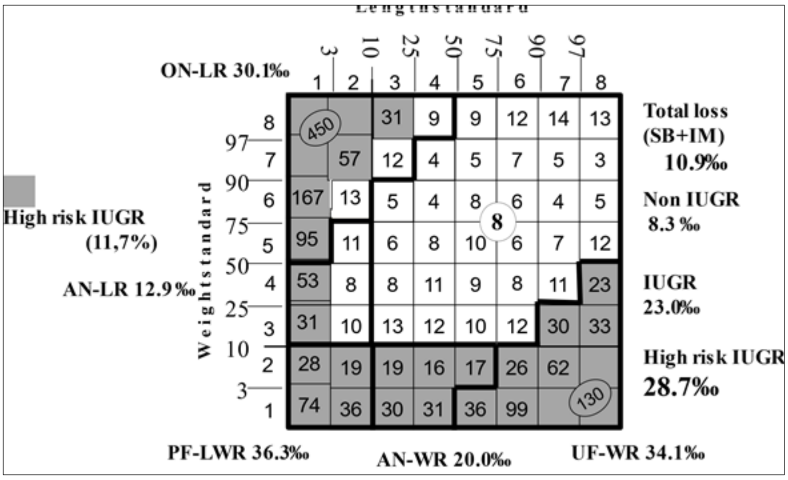

Figure 4 The stillbirth + infant mortality (SB+IM) values of the Hungarian newborn populace, 2000-2012. HR-IUGR cells were highlighted in a darker color

3. A new MDN-type growth restriction screening method

The MDN method is suitable for the IUGR screening of fetuses and neonates. Using this method, it can be identified whether the infant has an IUGR phenotype as well as the specific type of said phenotype. It can also be identified whether the infant falls into one of the high-risk (HR-IUGR) cells of the matrix. This is important, since HR-IUGR fetuses and neonates require immediate neonatological examinations after screening.

3.1. The IUGR screening method of neonates

Since neonatologists and pediatricians publish newborn and infant mortality rates as per mille values of total live births, another MDN percentile matrix was made, the cells of which represent the values of Hungarian infant mortalities. The matrix was made using the data of 1,238,891 live births recorded in Hungary during 2000-2012. With aid from the Hungarian Central Statistical Office, the development of each infant was followed for one year. Infant mortality data is not presented since, as mentioned before, the occurrence of IUGR was noticeably high even among late infant mortality cases.

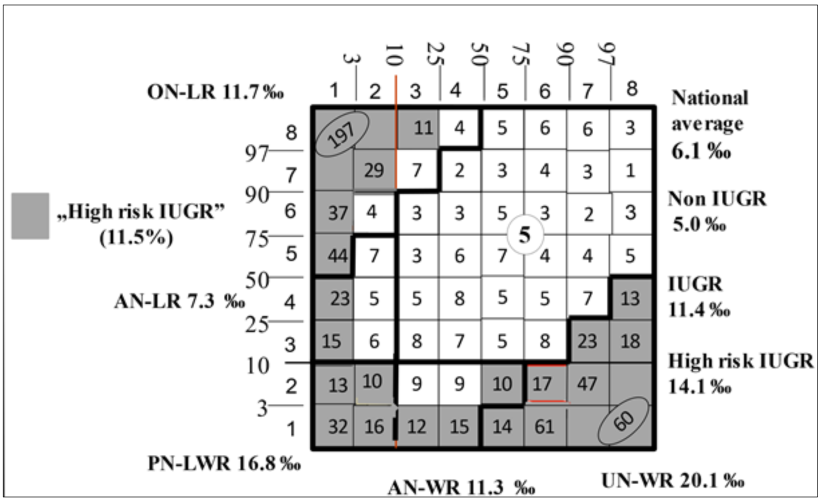

Figure 5 Hungarian infant mortality rates (2000-2012) on the MDN percentile matrix, showcasing both individual cell and IUGR subtype specific values

Out of all IUGR phenotype neonates only those were considered 'high-risk IUGR' whose cells had mortality rate values that are twice as high or even greater than the average mortality rate of the non-IUGR group, which is 5‰. The cells of 'high-risk IUGR' neonates on *Figure 5* are highlighted in grey [23, 24].

The results speak for themselves: the rate of infant mortality is 5.0‰ for the non-IUGR group, 11.4‰ for all IUGR types on average and 14.1‰ in the case of high-risk IUGR types, which is extremely high. The undernourished, weight restricted (UN-WR) and the proportionately nourished, length and weight restricted (PN-LWR) phenotypes have the highest mortality rates (20.1‰ and 16.8‰, respectively).

A specialized software was developed, which, following the input of four data points (gestational age, gender, weight and length) immediately highlights the corresponding cell of the infant on the MDN percentile matrix with a circle.

3.2. The purpose of MDN type screenings and the responsibility of neonatologists

It bears repeating that the purpose of the aforementioned screening method is not to provide error-proof means to identify fetuses and neonates with an IUGR condition, as that is only possible through diagnostic examination. The primary function of the screening is to identify whether the infant falls into a group where, due to an increased number of IUGR cases, the risk of infant mortality is significantly higher than average. Fetuses and neonates that fall into such categories must undertake immediate differential diagnostic examinations, in order to confirm whether they actually suffer from an IUGR condition, in which case optimal treatment of said condition may commence. The use of IUGR screenings followed by immediate neonatological examination and therapy could reduce the number of infant mortality cases. Furthermore, the timely identification and treatment of growth restriction could also mitigate the occurrence rate of childhood and adult conditions related to IUGR [25, 26, 27, 28, 29, 30].

4. The MDN type AC/FL ultrasound screening method of foetuses

Regrettably there were no screening methods in the past that could accurately identify growth restriction, along with the type and risk of IUGR during pregnancy. However, the use of the MDN method could provide a solution in this regard as well.

4.1. The issues with current IUGR ultrasound screenings

Currently, ultrasound screenings include the measurement of BPD, HC, AC and FL values, after which the software calculates which week's 50th percentiles each of the parameters correlate to [31, 32]. This method assumes that only values at the 50th percentile are considered 'normal'. However, that cannot be further from the truth.

We believe that instead of gestational age, ultrasound software should calculate which of the eight respective standard zones do each of the measured parameters fall into and whether those are significantly lower than the 50th percentile value.

4.2. Proposal to introduce MDN type AC/FL ultrasound screening

Ideally, the precise weight and length of the fetus could somehow be measured during pregnancy. However, such methods are unavailable at the time of writing, therefore one has to rely on the measurement of the abdominal circumference (AC) and femur length (FL), since these values correlate best with weight and length [32, 33, 34, 35, 36]. The measurement of said values is made possible with the use of state of the art equipment and plenty of patience and care on the doctor's behalf. The next step is to establish AC and FL standard positions, in order to determine which AC and FL zones a given fetus falls into (<3rd percentile = zone 1; 3-10th percentile = zone 2… >97th percentile = zone 8, etc.). Fortunately, a reliable source of AC and FL standards are available through the World Health Organization (*Torvid Kiserud, Gilda Piaggio, Guillermo Carroli et al*), which utilizes data gathered from 10 countries. These standards were also incorporated into our screening software [37].

Of course precise measurement of the weight and length of the fetus is not possible through AC and FL values alone. However, these values correlate the most with the weight and length of the fetus, therefore it can be assumed that AC and FL standard positions also correlate with the actual weight and length standard positions. A fetus is considered high-risk if the SB+IM value found in its cell is at least twice greater than the average SB+IM value (8.3‰) of non-restricted fetuses.

The following information can be inferred from *Figure 4*: 1. The SB+IM risk of the cell where the fetus belongs to, based on AC and FL screenings. 2. Whether the fetus has IUGR, and if yes, which specific type of it. 3. Most importantly, it can be determined whether the fetus falls into the category of "high-risk IUGR" fetuses or not. Fetuses in these categories might only have an IUGR phenotype (they are smaller in size due to their genetic makeup) but it also could be due to an IUGR condition. Since this cannot be determined precisely through ultrasound screening alone, the mothers all fetuses that fall into these cells should be admitted to hospital and undergo intense monitoring (NST, Doppler ultrasound screenings).

The SB+IM rate of non-restricted fetuses and neonates is 8.3‰. In the case of IUGR fetuses and neonates, the rate is 23.0‰ and it is higher among the high-risk IUGR group, 28.7‰. Certain individual cells may have even higher mortality rates.

On the MDN percentile matrix of stillbirths, the mortality rate of the non-IUGR group is merely 3.3‰. For the IUGR group, the mortality rate is 11.8‰ and for the high-risk IUGR group, it is 14.9‰. Several individual cells show extreme mortality rates. The mortality rates of specific types of IUGR on this MDN percentile matrix include the following values: ON-LR 18.6‰, AN-LR 5.7‰, PN-LWR 19.9‰, AN-WR 10.2‰, UN-WR 14.2‰.

The use of an MDN percentile matrix showcasing both stillbirth and infant mortality rates (SB+IM) is considered more suitable, since IUGR infants face not only the risk of intrauterine fetal death but also the possibility of mortality after a successful live birth.

4.3. Recommended protocol for IUGR screenings and the following obstetric procedures

- Fetal IUGR screenings should be carried out more than once, since the IUGR condition can cause hypoxia at any time during pregnancy, which, if not identified in time, may lead to intrauterine fetal death. We recommend IUGR screenings to be carried out on the 28th, 32nd, 36th and 40th weeks of pregnancy, or even more often in the case of pathological pregnancy. As to why screenings should start so soon, here is the distribution of Hungarian intrauterine fetal deaths by gestational age during 2000-2012 (each value represents a percentage of the total number of mortalities): Weeks <24: 0.3%, Weeks 24-28: 27.7%, Weeks 29-32: 22.9%, Weeks 33-36: 25.0%, Weeks >36: 24.1%. Overall, 75.9% of all intrauterine mortalities occur before the 37th week, which means that screenings must be carried out prior to the last month of pregnancy [38].
- Once identified, the mother of the high-risk IUGR phenotype group (cell) fetus, having been properly informed of the condition, should be admitted to the maternity ward, where the fetus must be put under intensive monitoring (which involves 1-2 NST and 2-3 Doppler ultrasound screenings daily). If this is not possible, either due to hospital capacity or the patient's personal circumstances, it is recommended to perform outpatient monitoring every 1-2 days. This is necessary so that deceleration of fetal circulation and other symptoms of hypoxia could be identified in time [38, 39, 40, 41, 42, 43, 44]. Additionally, it is recommended to perform ultrasound biometry and examine the placenta and the amount of amniotic fluid every two weeks, in order to identify the potential signs of the IUGR condition's progression in time.
- If signs of the IUGR condition's progression (deteriorating flow metric index values, decreasing amniotic fluid, 'aging' placenta, decreased placental capacity, etc.) are observed, or the Doppler ultrasound screening shows signs of hypoxia (centralized circulation, block, reverse flow), immediate C-section operation must be performed in order to prevent intrauterine fetal death [38, 39, 40, 41, 42, 43, 44]. The operation could be delayed for a few days, however it is not advised as that increases the risk of further health decline for the fetus and neonate as well as the potential for mortality in late infancy, which could result in a lawsuit.
- If the deceleration rate of the circulation is minimal, the operation could be held off for a few days while still maintaining intensive monitoring. In such cases, steroid prophylaxis must be performed before the 34th week. However, if severe signs of hypoxia are observed, then the IUGR fetus must be delivered immediately through C-section, as their life is at risk.
- We need to emphasize that this methodology does not provide diagnostic degrees of accuracy. Its accuracy is on par with any other type of screening, such as mammography or cervical cytological examinations, where proper diagnosis can only be ascertained after histopathologic examination is performed. The main purpose of screenings is to narrow down the scope of people to those who actually do require additional diagnostic examinations later on.

4.4. The main reason for expanding the concept and definition of IUGR

Using the proposed expanded definition of IUGR reveals that 37.5% of all IUGR fetuses and neonates are located above the 10^{th} weight percentile and only 62.45% of them can be found below that. More importantly, 26.4% of all IUGR mortalities (both fetuses and neonates) were born with weight over the 10^{th} weight percentile. It is this 26.4% of infants that could be saved, should we abandon the current definition of 'IUGR =< 10^{th} weight percentile' in favor of a new, broader concept.

Nomenclature

IUGR – Intrauterine Growth Retardation/Restriction
SGA – Small for Gestational Age
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 results of our research can be summed up as follows:

- We believe that, using the data of 1,244,918 Hungarian live and stillbirths over a 13 year period, the MDN method proved that the physical development of an infant cannot be evaluated by the weight standard position alone. The gender, weight and length standard positions and the nourishment status of the infant must all be considered simultaneously.
- Having recognized this, a proposal was made in order to expand the definition of IUGR and to distinguish 5 separate types of IUGR. It was also confirmed that each type of IUGR affects the risk of stillbirth and infant mortality differently. Simultaneous weight and length restriction is the most common and the most dangerous condition, but subtypes where the rate of weight and length development significantly differ from each other also pose a great risk.
- We believe that the MDN method offers a realistic possibility for the screening of high-risk IUGR (HR-IUGR) fetuses and neonates.
- With the emergency C-section delivery of fetuses with an IUGR condition that show signs of hypoxia (confirmed through NST and Doppler ultrasound screenings) and the timely and professional neonatological treatment of HR-IUGR neonates, the lives of approximately 300,000 Hungarian, and several hundred thousand, if not million other fetuses and neonates worldwide could be saved annually

Compliance with ethical standards

Disclosure of conflict of interest

We declare that there is no conflict of interest on our part.

References

[1] Battaglia FC, Lubchenco LO. A practical classification of new-born infants by weight and gestation age. Pediatrics. 1967, 71: 159-70.

[2] Clifford SH. Postmaturity with placental dysfunction. Pediatrics. 1954, 44:1-7.

[3] Lubchenco LO, Hausmann C, Dressler M, Boy E. Intrauterine growth as estimated from liveborn birth weight data at 24–42 weeks of gestation. Pediatrics. 1963, 32: 793-799.

[4] Gruenvald P. Chronic fetal distress and placental insufficiency. Biol Neonate. 1963, 5: 215-220.

[5] Miller HC., Hassanein K. Diagnosis of impaired fetal growth in newborn infants. Pediatrics. 1971, 48: 511-515.

[6] Ott WJ. The diagnosis of altered fetal growth. Obstet Gynecol Clin North Am. 1988, 215: 237-263.

[7] Lin CC. Current concepts of fetal growth restriction. Obstet. Gynecol. 1998, 92: 1044-1051.

[8] American College of Obstetricians and Gynecologists. ACOG Practice Bulletin Number 12. Intrauterine Growth Restriction.Washington, DC; 2000.

[9] Mestyán Gy. Intrauterine malnutritio. In: Véghelyi P., Kerpel-Fronius Ö. Az újszülött. Akadémia Kiadó, Budapest 1986.

[10] Doszpod J. Abnormal development of fetus. In: Doszpod J. Az intrauterin magzat. Medicina, Budapest 2000.

[11] Figueras F, Gardosi J. Intrauterine growth restriction: new concepts in antenatal surveillance, diagnosis, and management. Am J Obstet Gynecol. 2011, 204, (4): 288-300.

[12] Unterscheider J, Daly S, Geary MP, et al. Optimizing the definition of intrauterine growth restriction: the multicenter prospective PORTO Study. Am J Obstet Gynecol. 2013, 208, (4): 290-291.

[13] American College of Obstetricians and Gynecologists. ACOG Practice Bulletin Number 134. Washington, DC, 2013.

[14] Balchin I, Peebles D. Fetal growth, intrauterine growth restriction and small-for-gestational-age babies. In: Rennie J, Rennie & Roberton's Textbook of Neonatology, 5th Edition, Elsevier. 2013.

[15] Maris G, Tate DL. Detection and surveillance of IUGR. Contemporary OB/GYN 2013, 58, (10): October 1.

[16] Pelleg D, Kennedy CM, Hunter SH. Intrauterine Growth Restriction: Identification and Management. Am Fam Physician, 1998 Aug; 1, 58 (2): 453-460.

[17] Berko P. Investigation of the occurrence, causes and consequences of retardation using the UFT system. [A retardáció előfordulásának, okainak és következményeinek vizsgálata az UFT-rendszer segítségével]. Kandidátusi disszertáció. Budapest: Magyar Tudományos Akadémia, 1992. [Hungarian]

[18] Berko P, Joubert K. Effects of physical development and nutrition on intrauterine and neonatal mortality. [A testi fejlettség és tápláltság hatása az intrauterin- és újszülött-halálo- zásra]. Orv Hetilap. 2006,147 (29): 1369-1375. [Hungarian]

[19] Berko P,Joubert K. The effect of intrauterine development and nutritional status on perinatal mortality. J Materno-Fetal Neonat M. 2009, 22, (7): 552-559.

[20] Berko P,Joubert K. The Effect of Intrauterine Development and Nutritional Status on Perinatal, Intrauterine and Neonatal Mortality: The MDN System. In: Ezechi OC, Pettersson KO (ed). Perinatal Mortality. Zagreb: InTech; 2012, p. 11-27.

[21] Joubert K. Standards of birth weight and length based on liveborn data in Hungary, 1990–1996. J Hung Gynecolog. 2000, 63: 155-163.

[22] Joubert K, Zsakai A, Berko P. Weight and height standards of Hungarian newborns born in 2000-2012 [A 2000-2012-benszületett magyar újszülöttek súly- és hosszstandardjai]. Demografia. 2016, 58, (2-3): 173-196. [Hungarian]

[23] Berkő P, Joubert K, Zsakai A. A proposal to expand the concept of intrauterine growth retardation and to introduce a novel IUGR screening test for neonates. [Javaslat az intrauterin növekedési retardáció fogalom-körének kibővítésére, és az újszülöttek újszerű, IUGR-szűrővizsgálatának bevezetésére]. Nőgyógyászati és Szülészeti Továbbképző Szemle 2020, XXII/1, 4-10. [Hungarian]

[24] Berkő P, Joubert K, Zsákai A, Wagner Gy. The concept of intrauterine growth retardation and its methods of “MDN screening” [Az intrauterin növekedési retardáció fogalma, és „ÉFT-szűrővizsgálati” módszerei]. Miskolci Egyetemi Kiadó, Miskolc, 2022. [Hungarian]

[25] Barker DJP, Gluckman PD, Goldfrey KM et al. Fetal nutrition and adult disease. Lancet 1993, 341: 938–941.

[26] Henriksen T. Foetal nutrition, foetal growth restriction and health later in life. Acta Pediatr (Suppl) 1999, 88, (429):4-8.

[27] Osmond C, Barker DJ. Fetal, infant, and childhood growth are predictors of coronary heart disease, diabetes, and hypertension in adult men and women. Environ Health Perspect 2000, 108 (suppl 3): 545–553.

[28] Goldfrey KM, Barker DJP. Fetal nutrition and adult disease. Am J Clin Nutr 2000, 71: 1344–1352.

[29] Barker DJ. Adult consequences of fetal growth restriction. Clin Obstet Gynecol. 2006, 49, (2): 270-283.

[30] Geva R, Eshel R, Leitner Y, Valevski AF, Harel S. Neuropsychological outcome of Children With Intrauterine Growth Restriction: A 9-Year Prospective Study. Pediatrics 2006, 118, (1): 91-100.

[31] Berkő P, Joubert K, Gardos E, Gyenis G. Effects of bodily development and nutritional status at birth on physical and mental development measured at age 18. Journal of Gynecology and Obstetrics 2014, 2, (6): 116-122.

[32] Yeh M, Bracerol L, Reilly K, Murtha L,Aboulafia M, Barron B, Ultrasonic measurement of the femur length as an index of fetal gestational age. Am J Obstet Gynecol 1982, 144: 519

[33] Hill LM, Breckle R, Gehrkig WC, OBrien PC. Use of femur length in estimation of femur weight. Am J Obstet Gynecol 1985, 152: 847.

[34] Ruth B, Goldstein MD, Roy AF, Simpson G. Pitfalls in Femur Length Measurements. Ultrasound Med 1987, 6: 203-207.

[35] Vintzileos AM, Campbell, et al. The ultrasound femur length as a predictor of fetal length. Obstet Gynecol. 1984 Dec, 64, (6): 779-82. PMID: 6390277

[36] 36. Hadlock FP, Deter RL, Harrist RB, Roecker E, Park SK. A date-independent predictor of intrauterine growth retardation: femur length/abdominal circumference ratio. AJR Am J Roentgenol. 1983, 141, 979–84.

[37] Torvid Kiserud, Gilda Piaggio, Guillermo Carroli et al. The World Health Organization Fetal Growth Charts: A Multinational Longitudinal Study of Ultrasound Biometric Measurements and Estimated Fetal Weight. PLoS Med. 2017 Jan; 14(1): e1002220. Published online 2017 Jan 24. doi: 10.1371/journal.pmed.1002220

[38] Berkő P, Nagy G, Zsoubert K, Zsákai A, Wagner Gy. A magzati növekedési retardáció haskörfogat (AC)- és combcsonthossz (FL)- alapozott, új ultrahang ÉFT-szűrővizsgálati módszere. Magyar Nőorvosok Lapja, 2021, 84/1. 27-32.

[39] Campbell S, Pearce JM, Hackett G, Cohen-Overbeek T, Hernandez C. Qualitative assessment of uteroplacental blood flow: early screening test for high-risk pregnancies. Obstet Gynecol 1986 Novg, 68, (5): 649-653.

[40] Truding BJ, Gilles WB, Cook CM. Uteroplacental blood flow velocity-time waveforms in normal and complicated pregnancy. Br J Obstet Gynaecol 1985 Jan, 92, (1): 39-45.

[41] Carrera JM, et al. Ultrasound and Doppler management of intrauterine growth restriction. DSJUOG. July-September 2010, 4, (3): 259-274.

[42] Gardosi J, Giddings S, Buller S, Southam M, Williams M. Preventing stillbirths through improved antenatal recognition of pregnancies at risk due to fetal growth restriction. Public Health. 2014, 128: 698–702.

[43] Mandruzzato G. Guidelines for intrauterine growth restriction and chronic fetal hypoxaemia. TMJ 2009, Vol. 59, No. 2 152-160

[44] Froen JF, Gardosi JO, Thurmann A, et al. Restricted fetal growth in sudden intrauterine unexplained death. Acta. Obstet. Gynecol. Scand 2004, 83: 801-807.