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Screening methods for fetuses and newborns who are at increased risk due to the probability of IUGR disease

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Abstract

In Part I of their two-part study, the authors presented the MDN method (Maturity, Development, Nourishment), which allows for the simultaneous examination and classification of the weight and length development as well as the nourishment status of neonates. To accomplish this, a 64-cell MDN percentile matrix was developed, which can be used to depict and examine all combinations of weight and length development, as well as nourishment status. The data of 1,244,918 Hungarian neonates born during 2000-2012 was added to this matrix, after which the occurrence rates of stillbirth (SB), infant mortality (IM) and Total Perinatal Mortality (SB + IM) were calculated for each cell. Using these results, the authors distinguished 5 separate types of IUGR. This method was considered to be suitable for the identification and screening of high-risk IUGR fetuses and neonates. In Part II, the author present the screening methods that can be used during pregnancy and after birth to identify high-risk IUGR phenotype fetuses and neonates who might suffer from an IUGR condition. Fetuses and neonates with an IUGR condition identified through these screenings require immediate obstetric and neonatal diagnostic and differential diagnostic examinations and therapy in order to save their lives.

Keywords: MDN method; Intrauterine Growth Retardation; Screening methods of IUGR; Ultrasound IUGR screening during pregnancy; IUGR screening of newborns

1. Introduction

In Part I of their two-part study, the authors explained the following: 1.) Why do they believe that relying only on weight development (weight <10th percentile) to characterize and classify the physical development and lack of growth (IUGR) of fetuses and neonates to be completely insufficient. 2.) Why they believe that the simultaneous consideration of the gestational age, gender, weight and length standard positions as well as the nourishment status (the Nourishment Index) would be an alternative with far more realistic and accurate alternative instead.

The MDN percentile matrix, developed by *P. Berkő and K. Joubert*, was introduced, which consists of 8 horizontal zones correlating to the 8 known zones of Hungarian birth weight standard, and 8 vertical columns correlating to the 8 known zones of Hungarian birth length standards. The MDN percentile matrix is therefore made up of an 8 by 8 layout of 64 cells, with a designated cell for every possible combination of weight development, length development and nourishment status. Nourishment status is characterized by the use of the Nourishment Index, using the following

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formula: NI = W-L. For example, if we take the number of the weight (W=7) and length (L=2) zones of the cell highlighted in yellow in Figure 1, its Nourishment Index is NI=+5 *(Figure 1).*

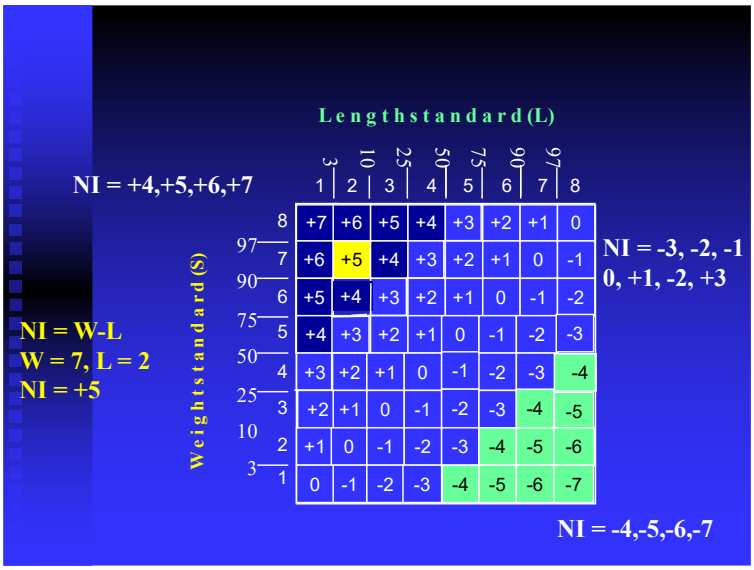

Figure 1 According to their nutritional status (their NI), newborns can be divided into 3 groups

It was proven with the use of the MDN method *(Figure 2)* that the rate of intrauterine fetal death and infant mortality cases not only increase due to a lack of weight development, but also in the case of a lack in length development, as well as in several other instances of disharmony between weight and length development [1-4].

The authors, put the standard positions of 1,244,918 Hungarian neonates (both live and stillbirths) on this matrix, then calculated the Total Perinatal Mortality (TPM = stillbirth + infant mortality) occurrence rates of Hungarian neonates born during 2000-2012 (per mille, rounded up). Taking the TPM results into consideration, a proposal was made to distinguish 5 separate types of IUGR (see Part I for a more detailed description) *(Figure 2).*

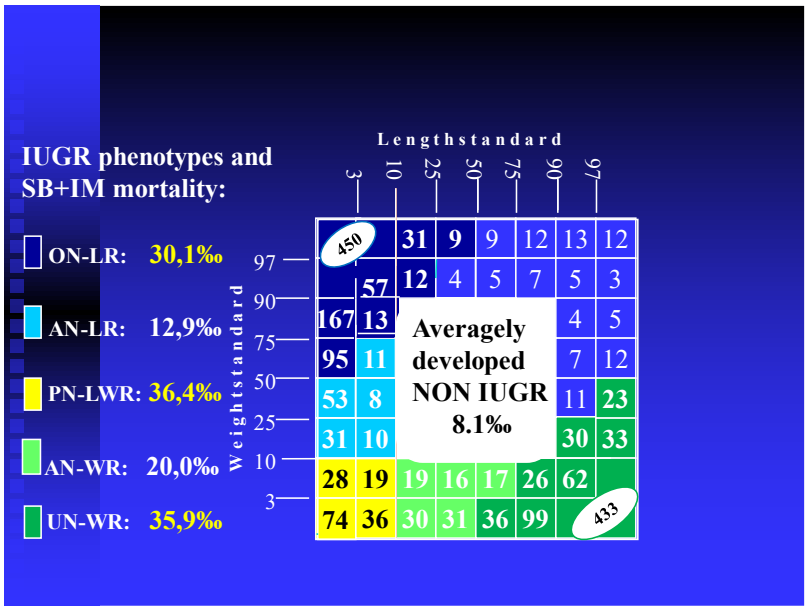

Figure 2 Separation of the 5 types of growth retardation (IUGR) and the rate of SB+IM mortality in each type of IUGR

The authors deemed the MDN (Maturity, Development, Nourishment) method that they have developed to be sufficient to distinguish between the different types of IUGR and to identify (screen) high-risk IUGR fetuses and neonates. Part II of their study presents the screening methods they have developed.

2. Methods

2.1. The IUGR screening of neonates

The IUGR screening of live neonates require an MDN percentile matrix where only the data on infant mortalities is showcased in each cell. Data on newborn mortalities is excluded as it was proven that IUGR still remains a significant factor in late infant mortality cases (the occurrence rate of IUGR is 42.3% among stillbirths, 29.7% among newborn mortalities and 37.4% among late infant mortalities).

Figure 3 showcases the average infant mortality rates of the various IUGR types (for example, ON-LR 11.5 ‰). The central white square of the matrix includes the average mortality rate of non-IUGR neonates (5.4‰). The TPM rate of IUGR phenotype neonates is 11.2‰ within the total population.

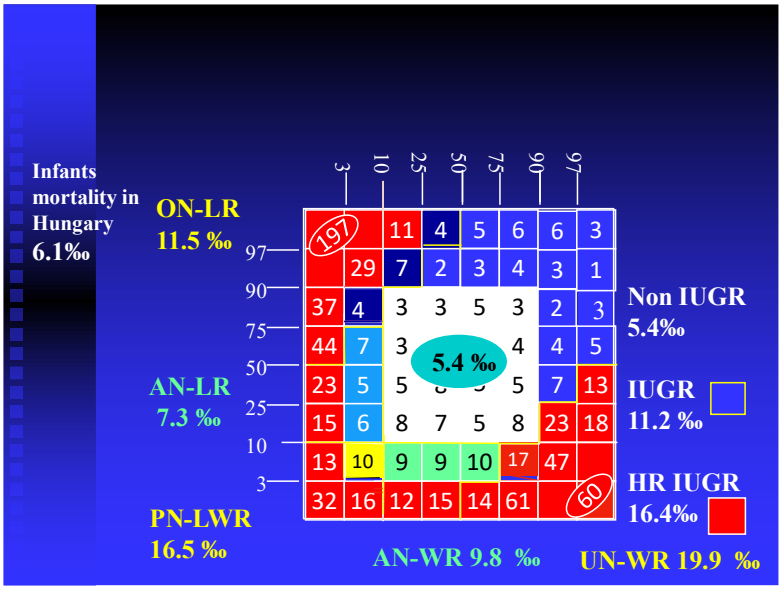

Figure 3 Infant mortality rates in the 5 types of IUGR and especially in the red cells of high-risk IUGR newborns in Hungary (2000-2012)

Within each type of IUGR we highlighted the cells of neonates that are considered to be at high-risk of an IUGR condition (HR-IUGR) in red. A neonate is considered to be at high risk if the TPM rate in its cell is twice as high as or greater than the average mortality rate of the non-IUGR group (5.4‰). The average rate of infant mortality among HR-IUGR neonates is 16.4‰ (three times higher than the average mortality rate of non-IUGR neonates).

Taking the aforementioned into consideration, we proposed the introduction and widespread adoption of the MDN type IUGR screening of neonates. The latter was recommended because the screening of high-risk IUGR neonates, followed by its confirmation via diagnostic examinations and the administration of appropriate treatment could, based on our data, save the lives 150 neonates suffering from an IUGR condition in Hungary each year.

2.1.1. The steps of neonate IUGR screenings

Step one: Using the table of nonspecific birth standards, made by Kálmán Joubert based on the data of 1,238,891 live Hungarian births [5], the weight and length standard positions of the neonate have to be determined. This is done by finding the number of the weight standard zone (W) that corresponds with the weight of the neonate (for example, in zone 7, meaning W = 7). The same must be done to determine the position of the length (L) standard position (for example, L = 2).

Step two: Using the MDN percentile matrix, the corresponding cell of the neonate has to be located. Each cell has a two-digit number associated to it, with the first digit referring to the W, and the second digit referring to the L value. Using the numbers given as examples in step 1, the cell number of the neonate is 72, in which the TPM rate is 29‰. This cell is part of the ONLR IUGR phenotype. The risk of mortality in this cell (29‰) is for times greater than that of the non-IUGR group (5.4‰).

Step three: Using Figure 2, the cell position of the neonate on the MDN percentile matrix has to be determined, followed by the corresponding TPM rate and IUGR type (if the neonate has an IUGR phenotype).

Step four: If the corresponding cell is red, the neonatologist colleagues must be notified, as these cases require additional diagnostic and differential diagnostic examinations as soon as possible to determine whether the neonate only has an IUGR phenotype, or they also suffer from an IUGR condition. This way, neonates with an IUGR condition can be saved and the risk of them developing related conditions later in childhood and adulthood can be mitigated.

The first three steps can be performed within a minute using a custom software that is available both in Hungarian and in English. After entering the gestational age, gender, weight and length values, the program displays the MDN percentile matrix, with the corresponding cell of the neonate highlighted.

Neonate IUGR screenings can be considered as the control examination of the IUGR screenings performed during pregnancy, which is especially relevant if a long period of time has passed between the last IUGR screening and the delivery of the infant.

2.2. The IUGR screening of fetuses during pregnancy

Many attempts were made to aid obstetricians in determining the physical development of fetuses and the identification of intrauterine growth retardation. There are two issues when it comes to such efforts: 1.) Since the definition of IUGR (IUGR = weight below the 10th weight percentile) only refers to a lack of weight development, colleagues performing ultrasound screenings could only estimate the weight of the fetus. However, no accurate method to do such a thing has been developed to this day. 2.) As we have proven previously, the knowledge of weight development alone is insufficient to properly diagnose IUGR. Therefore, even if a precise weighing method via ultrasound were to be developed, it would still not solve the problem of determining the exact type of IUGR.

2.2.1. The IUGR screening of fetuses based on AC and FL sizes correlating to weight and length and corresponding standard positions

It was a major issue for a long time that, even though the gestational age of the fetus was known, there were no precise means available to measure weight and length. Then, based on data from literature, it became apparent that in order to determine the development of a fetus, knowledge of the abdominal circumference (AC) and the femur length (FL) was sufficient enough, as these two values correlated the closest to weight and length. These values can be measured through ultrasound, however there were still no reliable AC and FL standards available [6-7].

Then the database of *Torvid Kiserud et al* [8] was published, which included data from 10 countries and multiple ethnicities, which were used to create international AC and FL standards (Table 2-3). We have been waiting for such standards for a long time, as it enabled us to develop an MDN screening method for IUGR which could be performed during pregnancy.

2.2.2. The steps of IUGR ultrasound screening

Step one: First, the gestational age of the fetus (measured in weeks) has to be known. Then, using ultrasound, the abdominal circumference (AC) and femur length (FL) has to be measured carefully and as accurately as possible.

Step two: Using the international AC and FL standards developed by *T. Kiserud et al*, the AC standard position of the fetus has to be determined (the standards are shared for boys and girls alike). For example, it is week 32 of the pregnancy, the AC value of the fetus is 280g and the FL value is 60mm. Using the AC standard, we can see that 280g falls between the 50th percentile value of 279g and the 75th percentile of 288g, which means it is located in AC zone 5. Therefore the weight value of the fetus in the Nourishment Index is W = 5.

Step three: The FL standard position of the fetus has to be determined. The FL value of the 32 week fetus in our example is 60mm, which is between the 25th percentile value of 59mm and the 50th percentile of 61mm, and located in the FL zone 4 (L = 4). Using the Nourishment Index formula (N = W-L), the nourishment index of the fetus is NI = W5 – L4 = +1 (based on the W and L values the fetus belongs to cell 54 of the MDN percentile matrix, see *Figure 2* in Part I).

Step four: Having identified the AC and FL standard positions, the fetus needs to be placed on an MDN percentile matrix where the horizontal rows are the AC standard zones and the vertical columns are the FL standard zones. Note the cell number of the fetus. Afterwards, the fetus has to be placed in the same numbered cell on an MDN percentile matrix

consisting of traditional weight and length zones, then it has to be checked if the fetus has IUGR, along with the specific type of IUGR and whether fetus is considered to be high-risk.

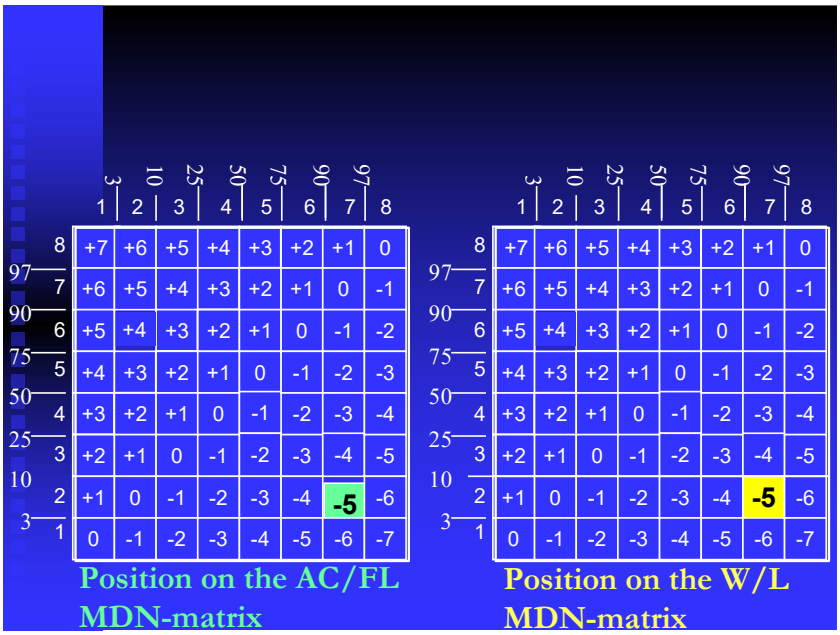

Figure 4 The Weight/Length matrix position of the fetus is "identical" with the AC/FL MDN matrix position of the fetus

The next image features another example: if the fetus is located in zone 15 on the AC/FL matrix, then it has to be placed in cell 15 of the weight/length matrix. This is an IUGR cell, within the UN-LR IUGR type.

Next, the TPM risk of cell 15 has to be checked. Figure 4 shows that the TPM risk rate of cell 15 is 62‰, therefore the fetus is considered a high-risk UN-LR fetus *(Figure 5)*

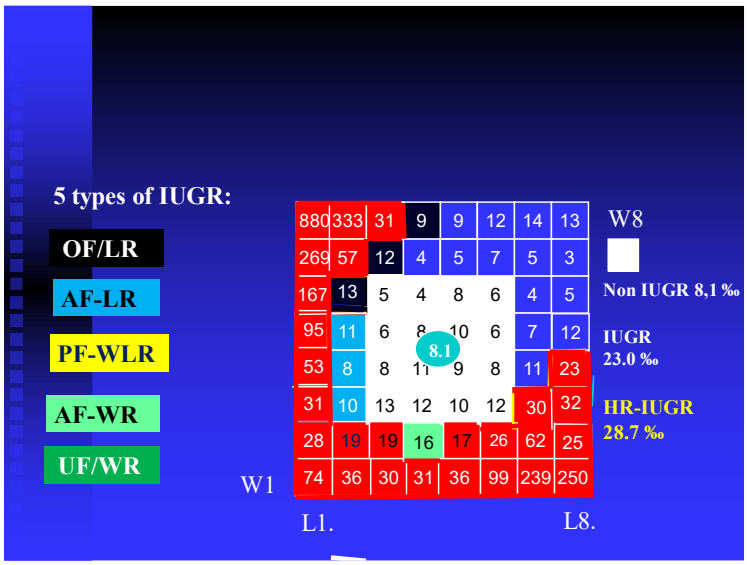

Figure 5 Risk of stillbirth + infant mortality for extremely endangered fetuses and newborns (TPM ‰)

The first four steps can be performed within a minute using a custom ***software*** that is available both in Hungarian and in English. After entering the gestational age, gender, weight and length values, the program displays the MDN percentile matrix, with the corresponding cell of the neonate highlighted.

If the examined fetus is considered to be high-risk based on the AC and FL values, then it is at risk of intrauterine fetal death or mortality at any period throughout infancy. Because of this, the cells of the MDN percentile matrix used for ultrasound screenings feature Total Perinatal Mortality results instead of merely stillbirth or newborn mortality-related ones.

Of course it also has to be considered that the AC/FL standard positions only represent the actual size of the fetus on that exact day. The more time passes between the last ultrasound screening and the delivery, the greater the discrepancy could become between the MDN percentile matrix position of the fetus determined during the screening and the actual MDN percentile matrix position of the newborn child. In such cases, the same procedure as for neonates has to be used to determine the correct MDN percentile matrix position.

It is interesting and instructive to compare the MDN percentile matrix positions of high-risk stillbirth and infant mortality cases. It is remarkable how similar the matrices of the two high-risk groups are. Both matrices prove that stillbirth and infant mortality are the highest in the cells of the 5 types of growth retardation *(Figure 6 and 7).*

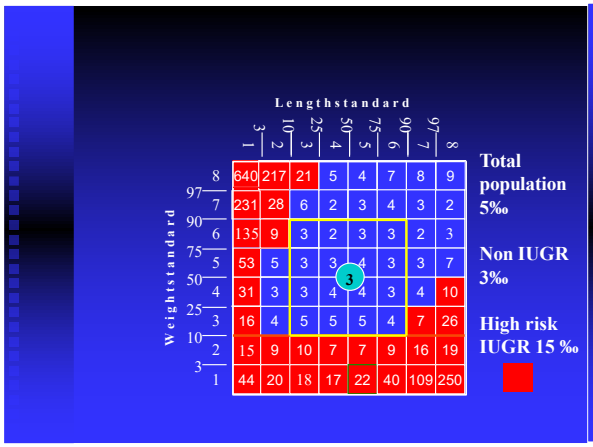

Figure 6 Stillbirth in total population

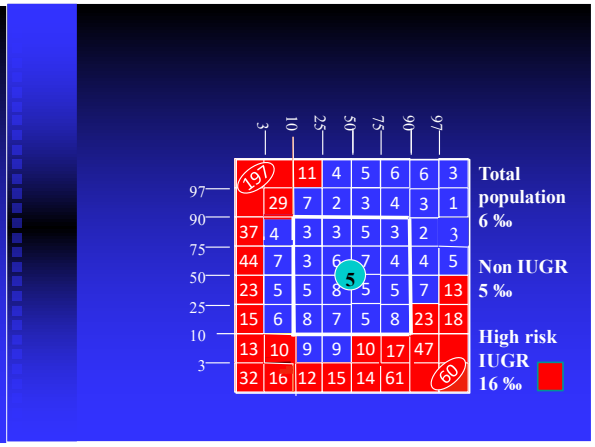

Figure 7 Infant mortality in total population

2.3. What to do if the fetus is considered high-risk IUGR based on the IUGR ultrasound screening

If the fetus is considered to be high-risk IUGR (Figure 3) based on the ultrasound screening, then the mother must be admitted to a hospital immediately, followed by regular intensive monitoring (at least 1 NST screening daily and at least 2 Doppler flowmetry daily).

If the resistance index rises above critical levels during Doppler flowmetry, or a decrease in prenatal circulation, block or reverse flow is determined, then immediate C-section delivery must be performed [3-4, 9-16]. Waiting can only gain us a few hours or a couple of days at most, however this increases the risk of intrauterine fetal death. Moreover, even if the fetus could be delivered alive, it is possible that it sustains internal organ damage during the wait period, which could either lead to infant mortality, or disease.

2.4. When and how often should IUGR ultrasound screenings be performed during pregnancy?

We recommend screenings to be performed on weeks 28, 32, 36 and 40. Why so often, and why at these intervals? We found that 0.3% of stillbirths occurred before the 24th week of pregnancy, and 27.9% occurred between the 24th and 28th weeks of pregnancy. During our examinations, we have found that **72.1%** of intrauterine fetal deaths in Hungary during 2000-2012 occurred after week 28 of pregnancy (weeks 29-32: **22.9%**; weeks 33-36: **25%**; week 36 or later: **24.1%**). Based on our calculations (and our definition), 42.3% of stillbirths (an annual average of 377 fetal deaths) were IUGR phenotype fetuses. Our task is clear: in order to save these children, we must use everything at our disposal to identify high-risk IUGR phenotype fetuses in time. To accomplish this, IUGR screenings have to be introduced and their use have to become widespread [3-4, 7].

3. Results

In the following, we present our research work, or the most interesting numerical results of our two-part thesis.

Table 1 Occurrences of stillbirth and infant mortality among 1,244,918 births in Hungary, between 2000 and 2012

number of total newborns	1 244 918		95 763/year
number of stillbirths	6027	(4,8‰)	464/year
number of live births	1 238 891		95 399/year
total number of infant mortality	7532	(6,1‰)	579/year
infant mortality between days 0 and 27	5032	(4,1‰)	387/year
infant mortality between days 28-364	2500	(2,0 ‰)	192/year
total number of mortalities (SB+IM)	13559	(10.9 ‰)	1043/year

Table 2 Abdominal circumference (AC) standards based on a multinational study *(T. Kiserud et al. 2017)*

Gestational weeks	28	29	30	31	32	33	34	35	36	37	38	39	40
8 zone	8	8	8	8	8	8	8	8	8	8	8	8	8
97,5 percentile	264	276	287	298	308	319	330	342	353	365	378	392	406
7 zone	7	7	7	7	7	7	7	7	7	7	7	7	7
90 percentile	256	266	277	287	298	308	318	329	340	352	364	377	391
6 zone	6	6	6	6	6	6	6	6	6	6	6	6	6
75 percentile	248	258	269	279	288	298	308	318	329	340	351	363	377
5 zone	5	5	5	5	5	5	5	5	5	5	5	5	5
50 percentile	240	250	260	269	279	288	298	307	317	328	338	350	363
4 zone	4	4	4	4	4	4	4	4	4	4	4	4	4
25 percentile	232	242	251	260	269	278	287	297	306	316	326	337	349
3 zone	3	3	3	3	3	3	3	3	3	3	3	3	3
10 percentile	225	234	243	252	260	269	277	286	294	304	313	324	335
2 zone	2	2	2	2	2	2	2	2	2	2	2	2	2
2,5 percentile	215	224	233	241	249	257	265	273	282	290	299	309	319
1 zone	1	1	1	1	1	1	1	1	1	1	1	1	1

Table 3 Femur length (FL) standards based on a multinational study *(T.Kiserud at al. 2017)*

Gestational weeks	28	29	30	31	32	33	34	35	36	37	38	39	40
8 zone	8	8	8	8	8	8	8	8	8	8	8	8	8
97,5 percentile	57	59	61	64	66	68	70	73	75	76	78	79	79
7 zone	7	7	7	7	7	7	7	7	7	7	7	7	7
90 percentile	55	57	60	62	64	66	68	70	72	74	75	76	77
6 zone	6	6	6	6	6	6	6	6	6	6	6	6	6
75 percentile	54	56	58	60	62	65	67	69	70	72	74	75	75
5 zone	5	5	5	5	5	5	5	5	5	5	5	5	5

50 percentile	52	54	56	59	61	63	65	67	69	70	72	73	73
4 zone	4	4	4	4	4	4	4	4	4	4	4	4	4
25 percentile	51	53	55	57	59	61	63	65	67	68	70	70	70
3 zone	3	3	3	3	3	3	3	3	3	3	3	3	3
10 percentile	49	51	53	55	57	60	61	63	65	67	68	69	69
2 zone	2	2	2	2	2	2	2	2	2	2	2	2	2
2,5 percentile	48	50	51	53	55	57	59	61	63	65	66	67	68
1 zone	1	1	1	1	1	1	1	1	1	1	1	1	1

Table 4 Evidence that IUGR significantly increases the incidence of stillbirths + infant mortality. - Deaths among 1,244,918 newborns born in Hungary in 2000-2012

Main groups	Total population	Stillbirth	Infant mortality	Newborn mortality	Late infant mortality
Non IUGR	8,1	3,4	5,0	3,5	1,5
IUGR	23,0	11,8	11,2	6,8	4,4
High risk IUGR	28,7	14,9	13,8	8,5	5,3
Total population	10,9	4,8	6,0	4,0	2,0

Table 5 SB+IM mortality (‰) of different IUGR types in Hungary (2000-2012)

Types of IUGR	Stillbirth	Newborn mortality	Late infants mortality	Total infant mortality	SB+IM
ON-LR	18.6	9.4	2.0	11.5	30.1
AN-LR	5.6	4.6	2.6	7.3	12.9
PN-LWR	19.9	9.5	6.9	16.5	36.3
AN-WR	10.2	5.5	4.3	9.8	20.0
UN-WR	14.2	16.2	3.6	19.9	34.1
Total IUGR mortality	11.8	6.8	4.3	11.2	23.0

4. Discussion

It was always evident to us that in order to evaluate physical development and define growth retardation (IUGR), relying solely on weight development was insufficient; therefore, we developed a new examination method (the MDN method). This methodology simultaneously considers weight development, length development and nourishment status. This was made possible with the aid of the MDN percentile matrix. Using this methodology and having processed the mortality data of 1,244,918 Hungarian neonates, it was possible and necessary to distinguish 5 types of intrauterine growth retardation. It was also pointed out that, in order to reduce the amount of intrauterine fetal death and infant mortality cases, high-risk IUGR fetuses and neonates need to be screened for and identified. To accomplish this, we developed methodologies for screenings that can be performed during pregnancy and on newborn infants. Part II of our study presented these two screening methods.

4.1. What are the possible benefits of the introduction and widespread application of IUGR screenings?

We highlighted why we believe having an IUGR phenotype and suffering from an actual IUGR condition must be differentiated and why high-risk IUGR fetuses and neonates must be identified and screened. On the one hand, this needs to be done since the majority of IUGR phenotype fetuses and neonates do not suffer from an actual IUGR condition and therefore do not require specific treatment. On the other hand, the identification and screening of high-risk fetuses and neonates is important because their lives depend on whether they receive the necessary obstetric care (intensive NST, Doppler flowmetry, and if needed, immediate C-section delivery) and neonatal diagnostic and differential diagnostic examinations as well as potential therapy once identified, which can prevent IUGR-related mortalities and the development of other medical conditions.

Having processed and evaluated the 13,559 (10.9‰) mortality cases out of the 1,244,918 Hungarian live and stillbirths recorded during 2000-2012 (13 years), there were a total of 3,907 cases (300 per year) of stillbirth or infant mortality where the fetus or neonate was considered as high-risk IUGR. If there were IUGR screening methods at the time, these cases could have been identified, examined (Doppler ultrasound) and delivered through C-section, or the necessary neonatal examinations and treatments could have been administered, which would have saved the majority of the 300 children each year who suffered from such conditions.

2/. We highlighted what could be gained by expanding the concept and definition of IUGR. Out of the previously mentioned 1,244,918 neonates born in a total of 13 years, 130,894 (10.5%) were considered to be IUGR phenotype neonates based on the classic definition (IUGR = weight below the 10th weight percentile). Using our proposed definition of IUGR, the number of neonates that could be considered having an IUGR phenotype increased to 215,303, raising the occurrence rate of IUGR to 17.3%. 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 10th 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 10th weight percentile. It is this 26.4% of infants that could be saved, should we abandon the current definition of 'IUGR =< 10th weight percentile' in favor of a new, broader concept.

Since the old definition has been in use (due to a lack of alternatives), in this 13-year period alone, a total of 84,409 IUGR fetuses and neonates (6,493 per year) failed to receive the necessary care and attention (24.1% of IUGR stillbirth and 28.7% of IUGR infant mortality cases had weight above the 10th weight percentile). This is something that should happen ever again. To put it in a different perspective, if the expanded definition of IUGR were to be used in the future, 6,493 fetuses and neonates would receive better care to prevent IUGR-related consequences in Hungary each year.

We believe that the introduction and general application of our proposed screenings would significantly reduce the number and frequency of IUGR related stillbirth (42.3%) and infant mortality (32.1%) cases. According to *Peleg D, Kennedy CM* and *Hunter SH* [17] the main reason of stillbirth is IUGR, and it is the second most common cause of infant mortality after prematurity. If IUGR screenings become widespread, the annual number of fetuses and neonates suffering from intrauterine growth retardation related conditions that can be saved is estimated to be in the millions. It all depends on us.

3/. Neonate IUGR screenings have another hypothetical benefit as well. Based on data from literature, it is possible that there is a cause and effect relation between IUGR and the risk of heart attack and type 2 diabetes mellitus in adulthood [18-23]. We will attempt to extend this research to cover several other major diseases. If such causations can be confirmed, then life-long lifestyle choices can be recommended to the parents of children with an IUGR condition, in order to prevent the potential development of serious conditions in adulthood.

5. Conclusions

The authors have developed a test method (MDN method) to classify the physical development of fetuses and newborns by simultaneously taking into account gestational age, weight and length development and nutritional status, and to distinguish between 5 types of fetuses and newborns with intrauterine growth retardation (IUGR phenotype).

Using this method, they have developed screening methods to detect fetuses and newborns with IUGR phenotypes at increased risk of IUGR disease. These screening tests can be performed in 1-2 minutes using software developed by the authors and can be used to identify those fetuses and newborns who urgently need to undergo fetal and neonatal IUGR diagnostic tests! If positive, IUGR affected fetuses should be delivered without delay and appropriate neonatal management of IUGR affected newborns should be carried out.

These MDN-type screening methods can help to save the lives of many IUGR fetuses and newborns.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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