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The concept of IUGR needs to be expanded, its definition clarified, and the 5 types of IUGR separated!

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Abstract

Part I of this two-part study presents the MDN method (Maturity, Development, Nourishment), which is an examination method that allows for the simultaneous examination and evaluation of the weight and length development, as well as the nourishment status of fetuses and neonates. The authors processed the data of 1,244,918 Hungarian neonates born over a 13-year period (2000-2012), which was provided by the Hungarian Central Statistical Office. The MDN percentile matrix created by the authors is an 8 by 8 grid consisting of 64 cells. The matrix has a dedicated cell for every possible combination of physical development. The Total Perinatal Mortality (TPM, stillbirth + infant mortality) value and the number of cases were calculated for each individual cell of the MDN-matrix. Through this process, it was determined that higher than average TPM occurs not only in the case of a lack of weight development, but also in the case of a lack of length development, as well as in the case of extreme conditions of nourishment. Based on the above, it was proposed to separate intrauterine growth retardation into 5 distinct types. The methodology was also deemed acceptable to be used during the screening of fetuses and neonates that are considered to be at high risk due to their intrauterine growth retardation (IUGR) condition.

Keywords: MDN method; IUGR types; IUGR screening; Stillbirth; Infant mortality

1. Introduction

I vividly recall the arguments we had back when I was a young obstetrician about whether it is correct that the concept and definition of prematurity is tied to the weight of the neonate (an infant is only considered premature if their weight is below 2,500 grams). Me and my colleagues also found it odd that the neonatologists determined how much risk neonates were facing based on weight groups (<500g, 500-1,000g, 1,000-1,500g, 1,500-2,500g and >2,500g). Afterwards, we became familiar with the concepts of SGA, dysmaturity, intrauterine growth retardation and intrauterine growth restriction (IUGR). At the time, and even today, these concepts were defined as such: 'the neonate is only affected by such conditions, if the weight value is below the 10th weight percentile.' All of these important definitions were based exclusively on weight development. Even though we still respect the colleagues who pioneered the research of these phenomena [1-13], we believe that we should move past this weight-centric approach and a change in perspective is needed.

On the subject of the naming of IUGR: We agree that simply referring to the lack of growth development of the fetus as 'retardation' is incorrect, as it can be confused with a lack of mental development, which can be both confusing and

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hurtful. However, the use of 'growth retardation' is still correct, and possibly even more expressive than the recently adopted (in English-speaking areas) term of 'growth restriction'. Therefore, we believe that the term 'growth retardation' should remain in use over 'growth restriction'. Should it require change in the future, we recommend the use of 'growth disorder' as a potential alternative.

We are certain however, that the concept and definition of IUGR should not be based on the sole criteria of weight development. It is evident to us that relying solely on weight development to determine overall physical development is insufficient. In our opinion, in order to properly evaluate physical development, the gestational age, gender, weight development, length development and nourishment status all need to be considered, as it provides opportunities for more complex characterization and classification [14]!

In the beginning of our research, we sought to find answers to the following questions:

- How can weight and length development, as well as the nourishment status be simultaneously considered, visualized and have results that can be expressed in numbers?
- How can we determine which types (and combinations) of weight development, length development and nourishment status have the greatest associated risk of stillbirth or infant mortality?
- What does IUGR mean? Shouldn't it be clarified whether a fetus or neonate is merely smaller in size, but otherwise healthy (IUGR phenotype), or actually suffering from an IUGR condition?
- Is it true that "IUGR disease", which threatens the death of both the fetus and the newborn, only occurs among those who are retarded in weight development, i.e. only among those who weigh less than the 10th weight percentile? If not, which types of IUGR phenotype fetuses and neonates should be distinguished?

How can the MDN method put to be use in clinical practice in order to identify high-risk IUGR fetuses and neonates early – in other words, can it be used for IUGR screenings?

In Part I of our two-part study we provide answers to questions 1-4. Question 5 will be answered in Part II.

2. Method

2.1. How can weight and length development, as well as the nourishment status be simultaneously considered, visualized and have results that can be expressed in numbers? - This complex task can be solved with the aid of the MDN method

To answer the aforementioned questions, the so-called MDN method was developed together with my co-authors. It was named as such to signify that in order to classify physical development, four parameters are required (outside of the neonate's gender): Maturity (gestational age), Development (weight and length standard positions) and Nourishment (nourishment index value). The gender of the neonate is necessary because the examination of boys and girls require separate sets of standards [14-18, 20-22].

In order to put the MDN method to use, first we required a reliable source of birth weight and length standards, based on a sufficient number of cases, in table format. These standards were compiled by co-author *Kálmán Joubert* [19, 23]. Our standards were made using the data of 1,238,891 live births from 2000-2012, which was provided by the Hungarian Central Statistical Office. A separate set of standards were made for boys and girls (see Tables 1-2 and 3-4 at the end of Part I). The standards consisted of 8-8 zones respectively, separated by the 3rd, 10th, 25th, 50th, 75th, 95th and 97th percentile lines (curves), with zone 1 located below the 3rd percentile and zone 8 located above the 97th percentile.

Table 1 Weight standards for the Hungarian male neonates born between 2000 and 2012

Gestational weeks	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41
8 zone	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8
97 percentile	1296	1483	1690	1916	2159	2414	2675	2937	3192	3440	3676	3899	4101	4277	4435	4561
7 zone	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
90 percentile	1156	1323	1508	1711	1930	2162	2403	2648	2893	3134	3368	3591	3795	3973	4128	4269
6 zone	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
75 percentile	1029	1178	1343	1525	1723	1935	2157	2387	2621	2856	3088	3310	3515	3694	3847	3964
5 zone	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
50 percentile	899	1030	1175	1336	1511	1702	1905	2119	2342	2569	2798	3020	3225	3405	3555	3688
4 zone	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
25 percentile	774	888	1014	1154	1308	1478	1662	1861	2072	2292	2517	2738	2943	3123	3270	3399
3 zone	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
10 percentile	663	761	870	991	1126	1277	1444	1628	1828	2041	2261	2480	2686	2865	3009	3114
2 zone	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
3 percentile	549	631	723	825	941	1072	1221	1390	1578	1782	1998	2214	2418	2596	2738	2838
1 zone	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1

Table 2. Length standards for the Hungarian male neonates born between 2000 and 2012

Gestational weeks	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41
8 zone	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8
97 percentile	42,6	44,0	45,5	46,9	48,3	49,7	51,0	52,2	53,4	54,5	55,6	56,6	57,7	58,6	59,3	59,9
7 zone	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
90 percentile	40,0	41,4	42,9	44,3	45,8	47,2	48,6	49,9	51,2	52,4	53,5	54,6	55,7	56,6	57,3	58,0
6 zone	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
75 percentile	37,6	39,0	40,5	42,0	43,4	44,9	46,3	47,7	49,0	50,3	51,5	52,7	53,8	54,7	55,4	55,9
5 zone	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
50 percentile	35,1	36,6	38,0	39,5	41,0	42,5	43,9	45,4	46,8	48,2	49,5	50,7	51,8	52,7	52,3	53,8
4 zone	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
25 percentile	32,7	34,2	35,7	37,1	38,6	40,2	41,7	43,2	44,7	46,1	47,5	48,7	49,8	50,7	51,4	51,7
3 zone	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
10 percentile	30,7	32,1	33,6	35,1	36,6	38,1	39,6	41,2	42,8	44,3	45,7	47,0	48,1	49,0	49,6	50,0
2 zone	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
3 percentile	28,6	30,1	31,5	33,0	34,5	36,1	37,6	39,2	40,8	42,4	43,9	45,2	46,3	47,2	47,8	48,3
1 zone	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1

Table 3 Weight standards for the Hungarian female neonates born between 2000 and 2012

Gestational weeks	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41
8 zone	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8
97 percentile	1262	1446	1651	1875	2114	2364	2617	2865	3105	3336	3556	3762	3949	4110	4252	4363
7 zone	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
90 percentile	1114	1277	1459	1658	1873	2099	2333	2567	2799	3027	3248	3457	3648	3812	3953	4061
6 zone	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
75 percentile	983	1127	1288	1465	1658	1863	2079	2300	2525	2749	2970	3182	3375	3541	3681	3796
5 zone	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
50 percentile	850	976	1116	1270	1440	1625	1822	2029	2245	2465	2685	2898	3093	3262	3400	3501
4 zone	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
25 percentile	726	834	954	1087	1236	1400	1579	1773	1979	2194	2413	2626	2822	2992	3129	3226
3 zone	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
10 percentile	617	709	811	926	1056	1201	1364	1545	1742	1952	2168	2380	2577	2748	2883	2966
2 zone	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
3 percentile	508	585	670	767	877	1004	1150	1316	1503	1706	1918	2129	2326	2497	2629	2708
1 zone	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1

Table 4 Length standards for the Hungarian female neonates born between 2000 and 2012

Gestational weeks	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41
8 zone	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8
97 percentile	42,6	44,0	45,3	46,7	48,1	49,4	50,6	51,8	52,9	54,0	55,0	56,0	56,9	57,7	58,4	59,4
7 zone	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
90 percentile	39,9	41,3	42,7	44,1	45,5	46,8	48,2	49,4	50,6	51,8	52,9	53,9	54,9	55,7	56,4	56,9
6 zone	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
75 percentile	37,4	38,8	40,2	41,6	43,0	44,5	45,8	47,2	48,5	49,7	50,9	52,0	53,0	53,8	54,5	55,1
5 zone	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
50 percentile	34,8	36,2	37,6	39,1	40,5	42,0	43,4	44,8	46,2	47,6	48,8	50,0	51,0	51,9	52,5	53,0
4 zone	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
25 percentile	32,4	33,8	35,2	36,6	38,1	39,6	41,1	42,6	44,0	45,5	46,8	48,0	49,1	49,9	50,6	51,0
3 zone	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
10 percentile	30,2	31,6	33,0	34,5	36,0	37,5	39,0	40,6	42,1	43,6	45,0	46,3	47,4	48,2	48,9	49,3
2 zone	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
3 percentile	28,1	29,5	30,9	32,4	33,8	35,4	36,9	38,5	40,2	41,7	43,2	44,5	45,6	46,5	47,1	47,4
1 zone	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1

2.2. The consecutive steps of using the MDN method

Step one – the weight and length standard positions of the neonate have to be determined: After delivery, the gestational age and gender of the neonate have to be checked, then their weight and length have to be measured. Based on these measurements, the corresponding weight and length standard zones of the neonate can be determined. For example, the weight corresponds with zone 7 (W = 7) and the length corresponds with zone 3 (L = 3) *(Tables 1-4).*

Step two – Having identified the standard positions, the examined neonate has to be placed on the MDN percentile matrix. The horizontal rows of the matrix represent the 8 weight standard zones (W), and the vertical columns represent the 8 length standard zones (L). The matrix has a total of 64 cells, and we have to find in which cell does the neonate belong *(Figure 1).* The cells of the matrix are named after the numbers of the W and L zones, which means that our neonate from the previous example is located in cell 73 *(Figure 1).*

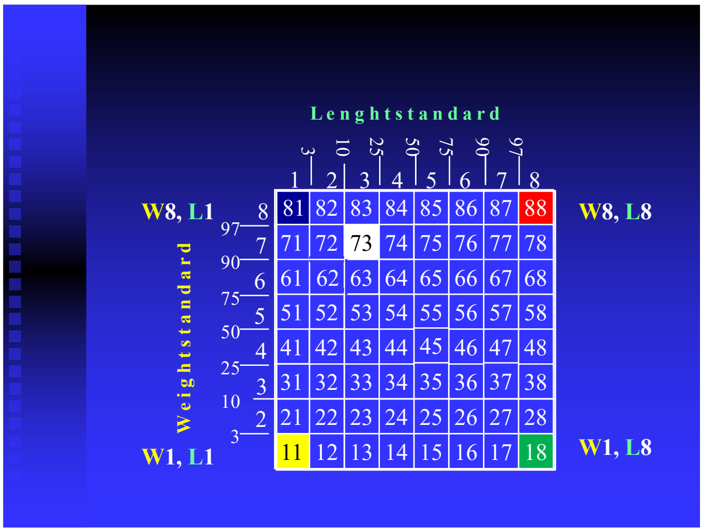

Figure 1 The weight and longitude zones on the matrix, the names of the cells, and the positions of the 4 most extreme developmental states

Step three – The nourishment status of the neonate has to be determined. Since nutritional status refers to the relation between weight and length, the Nutritional Index (NI) value of the neonate can be gained by subtracting the number corresponding to length (L) from the number corresponding to weight (W). If the value is positive, the neonate is considered relatively overnourished. If the NI = W-L value is negative, the neonate is considered undernourished.

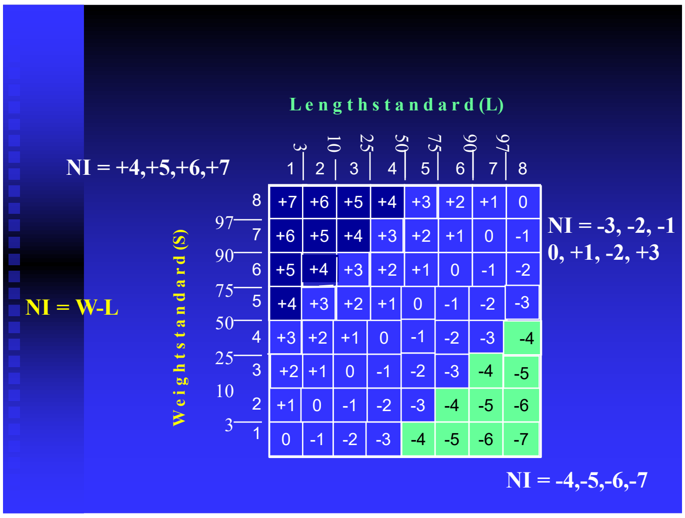

Figure 2 According to their nutritional status (their NI) newborns can be divided into 3 groups

Neonates with an NI value of -3, -2, -1, 0, +1, +2, or +3 are considered to be *averagely nourished*. Neonates are considered *overnourished* (compared to their length) if their NI value is +4, +5, +6, or +7. Neonates with an NI value of -4, -5, -6, or -7 are considered to be *undernourished* (*Figure 2*).

Note: We believe that the Hungarian birth standards are based on a sufficiently large number of cases and are suitable for use in countries where the majority of the population have similar physical characteristics. However, in the case of countries where the physical measurements of neonates differ significantly, we recommend the creation and usage of a more specific set of standards.

3. Results and discussion

3.1. How can we determine which types (and combi-nations) of weight development, length development and nourishment status have the greatest associated risk of stillbirth or infant mortality?

Following the development of the MDN percentile matrix, co-author *Annamária Zsákai* [23] calculated the rates of stillbirth and infant mortality cases of Hungarian neonates born during 2000-2012 for each cell of the MDN percentile matrix, as per mille values. Since it was later recognized that the number of mortality cases among IUGR neonates was still major between day 27 and age 1, Total Perinatal Mortality (TPM, based on the combined number of stillbirths and infant mortalities) values were also calculated for each cell (*Figure 4*). TPM values were also calculated for each weight and length zone of the MDN percentile matrix as well as for all possible nourishment statuses (*Figures 3-4*).

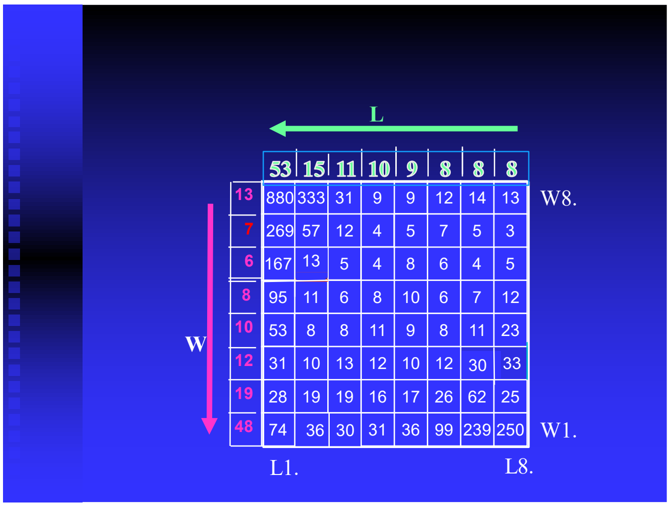

Figure 3 Stillbirth + Infant Mortality (TPM = SB+IM ‰) in the cells and zones of MDN-percentile matrix

The purple numbers in Figure 4 represent the TPM rates of the individual weight zones (from 7‰ up to 48‰). The TPM rate increases as the number of the weight zones become lower. The green numbers represent the mortality rates of the individual length zones. The TPM rate increases as the number of the length zones become lower (from 8‰ up to 53‰).

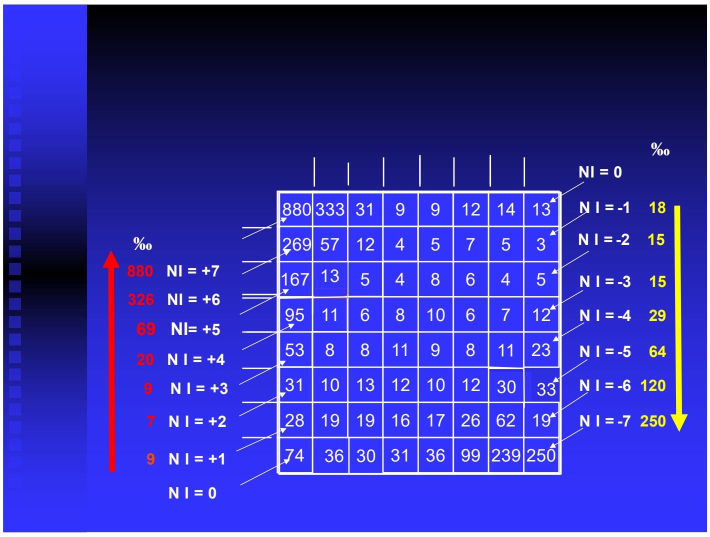

Figure 4 The importance of nutritional status for TPM in the cells and zones of MDN-percentile matrix

Figure 5 shows that the more undernourished the neonate is (NI = -2 to -7), the greater the TPM value becomes (from 15‰ up to 250‰). Similarly, the more overnourished the neonate is (their weight exceeding their shorter length, NI = +2 to +7), the greater the TPM value becomes (from 7‰ up to 880‰).

We believe that the TPM values in the cells of *Figures 3 and 4* prove that higher than average mortality rates are not exclusive to cases where the weight is below the 10th weight percentile and can also occur in other cases where there is a lack of physical development. This means however, that the current concept and definition of intrauterine growth retardation (IUGR) has to be reconsidered. [24-27]

3.2. What types of IUGR should be distinguished, and how to expand the concept and definition of IUGR?

Having taken the results of stillbirth + infant mortality (TPM) results into consideration, we distinguished 5 separate, characteristically different types of IUGR (highlighted on the matrix using different colors).

3.2.1. IUGR types and their associated TPM-rates

(occurrence rates within the population in brackets, in percenttages) **TPM**

AN-WR - Averagely nourished, Weight Retardált **(5.4%) 20.0‰**

(only weight development is lacking, below the 10th percentile)

AN-LR – Averagely Nourished, Length Retardált **(5.8%) 12.9‰**

(only length development is lacking, below the 10th percentile)

PN-LWR – Proportionaly Nourished, Length and Weight Ret**.(4.7%) 36.4‰**

(both weight and length both are lacking, below the 10th percentile)

UN-WR – Undernourished, Weight Retardált **(0.7%)** **35.9‰**

(weight is underdeveloped compared to length, NI = -4 to -7)

ON-LR – Overnourished, Length Retardált **(0.9%) 30.1‰**

(length is underdeveloped compared to weight, NI = +4 to +7)

(Non-IUGR group: TPM = 8.1‰)

The following MDN percentile matrix includes the rounded up TPM values of each cell. The average TPM values for each specific type of IUGR are also featured to the left of the matrix *(Figure 5).*

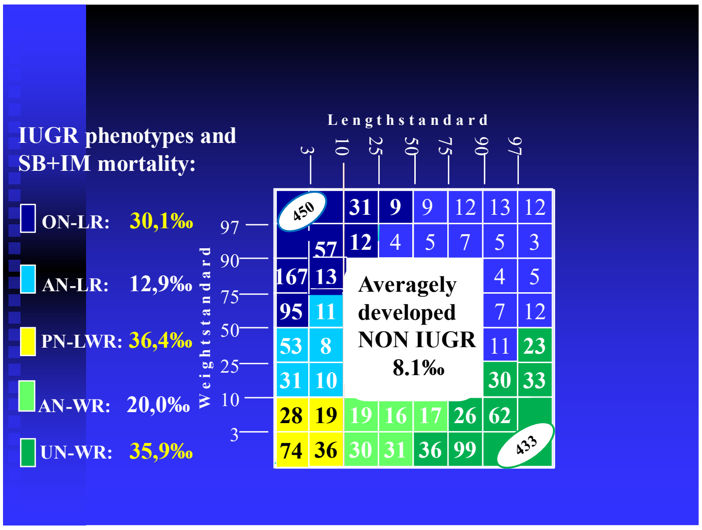

Figure 5 You can see the separation of the 5 types of growth retardation (IUGR) and the rate of SB+IM mortality in each type of IUGR

The current definition of IUGR (IUGR = weight below the 10th weight percentile) only applies to 16 cells of the matrix, which is only 10.5% of all neonates born in the examined 13-year period. If we add the number of IUGR neonates located in the 18 IUGR cells above the 10th weight percentile (6.9%), then, using our definition, it can be stated that among the Hungarian neonate population born during 2000-2012 (a total of 1,244,918 cases of live and stillbirths), *17.4% had an* IUGR phenotype*.*

3.3. Among the types of IUGR that we separate, significant differences can be discovered between the frequency of occurrence and degree of danger of each type

The most frequent occurrences are AN-LR (5.8%), AN-WR (5.4%) and PN-LWR (4.7%), while the occurrence of the ON-LR type is only 0.9%, and the occurrence of UN-WR is only 0.7%.

The most dangerous are PN-LWR (TPM: 36.4‰), UN-WR (TPM: 35.9‰) and ON-LR (TPM: 30.1‰), while the TPM of AN-WR is only 20.0‰, the TPM of AN-LR its value is only 12.9‰.

In summary: since the PN-LWR type is one of the most common (4.7%), and it is also associated with the highest TPM value (35.9‰), this is the biggest concern for obstetricians and neonatologists.

3.4. It is most important to isolate "highly-risked IUGR" fetuses and newborns!

We originally tried to create symmetry on the MDN percentile matrix when separating the individual IUGR types. A more thorough analysis reveals however that there are IUGR types where, in addition to cells with higher risk of mortality, there are also cells with only average mortality rates.

Therefore, we decided to highlight cells within each type of IUGR where the TPM values are twice as high as or greater than the value of the non-IUGR group's average mortality rate (8.1‰). Fetuses and neonates located in such cells are considered to be 'high-risk IUGR' types (Figure 6), who require additional examinations of diagnostic accuracy. This allows for the proper identification of fetuses and neonates suffering from an IUGR condition.

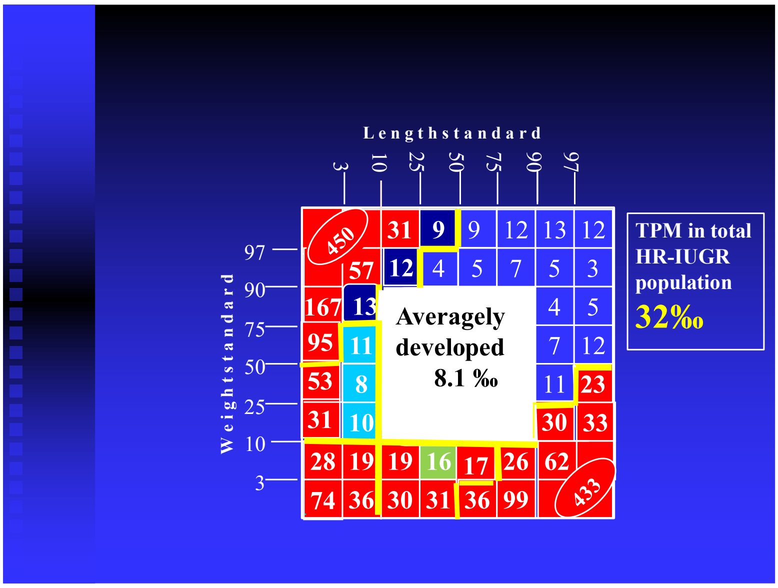

Figure 6 You can see the separation of the 5 types of growth HR-retardation (HR-IUGR) and the rate of SB+IM mortality in each type of IUGR

3.5. The previously shown examinations and mortality rate results clearly highlight that there needs to be a differentiation between IUGR phenotypes and the actual IUGR condition

We must admit that when using the term IUGR, it can be often unclear what we are thinking of. Do we only mean cases where the weight is below the 10th percentile, our proposed definition (one of the IUGR types based on the MDN method) or that the neonate has an IUGR phenotype and also suffers from an IUGR condition? These are all vastly different things. Each cell of the MDN percentile matrix (save for a few with extreme high mortality rates) ‘only’ has a mortality rate of 20-30‰ (2-3%), which means that the majority of these cells include neonates with an IUGR phenotype who are otherwise healthy. Therefore it is important to differentiate between IUGR phenotype neonates and neonates who actually suffer from an IUGR condition.

It is therefore important to distinguish between newborns with only the IUGR phenotype, but not sick, and those with the IUGR phenotype, but at the same time with IUGR! The purpose of IUGR screening tests is precisely to be able to recognize in time: whether the newborn belongs to a cell where the occurrence of stillbirths or infant deaths is significantly higher than average. Because if it is, then additional, now diagnostic, tests will be needed in order to recognize the probable IUGR disease as soon as possible. If these confirm the IUGR disease, adequate therapeutic intervention will be necessary to prevent the death of the fetus or newborn.

4. Conclusion

The development of the MDN method made it possible to prove that in order to evaluate and classify physical development or a lack thereof, relying solely on the knowledge of the weight and the weight standard value is insufficient. In addition to the gestational age, gender and weight, length and nourishment status must also be considered simultaneously. The MDN percentile matrix developed by the authors provides a good opportunity for that.

By using the data of a vast number of patients (1,238,891 Hungarian live births), the authors developed reliable birth weight and length standards. Afterwards, the data of 1,244,918 live and stillbirth cases were added to the MDN percentile matrix, which resulted in them making sufficiently reliable findings. By examining the occurrences of cases of stillbirth, infant and perinatal mortalities for all possible combinations of physical development in the 64 cells of the MDN percentile matrix, it became apparent that higher than average mortality rates were not exclusive to cells located below the 10th weight percentile. This led to the notion to change the concept and definition of intrauterine growth retardation that is currently used worldwide. It was proven that higher than average rates of mortality occur in 5 distinct states of physical development, therefore it was recommended to distinguish 5 separate types of IUGR.

Considering that the majority of the mortality rates in the cells of IUGR neonates are per mille values, it is evident that the overwhelming majority of IUGR fetuses and neonates do not suffer from an actual IUGR condition. Presumably, these children have only inherited the physical characteristics of their race and parents, therefore their smaller measurements are not symptoms of a condition but genetically determined. Such cases are considered to have an IUGR phenotype. However, if fetuses and neonates showcase symptoms during labor and after birth, those have to be considered as cases of an IUGR condition. It is important to distinguish these two. Unfortunately, there are no currently available opportunities or methodologies to perform examinations with diagnostic accuracy on all fetuses and neonates that are deemed smaller than average. We need screenings that are specifically designed to narrow down the number of cases that truly require diagnostic examinations. The authors developed two such *screening methods, which will be presented in Part II*

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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