# Microcephaly at birth - the accuracy of three references for fetal head circumference. How can we improve prediction?

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**Abstract**

OBJECTIVE: To evaluate the ability to predict microcephaly at birth (MICB) by using the conventional and two new prenatal references for fetal head circumference (HC). To assess whether integrating additional parameters can improve prediction.

METHODS: Microcephaly in utero was defined as a fetal head circumference 3 standard deviations (SD) below the mean for gestational age according to Chervenak et al's reference (CR). The records of cases with fetal microcephaly (FMIC) were evaluated for the medical history, imaging findings, biometry, and postnatal examination/autopsy findings. Microcephaly was confirmed at birth by an occipitofrontal circumference (OFC) or a brain weight at autopsy 2SD below the mean for gestational age. The new INTERGROWTH-21$^{st}$ Project (I21P) and a recent Israeli reference (IR) for fetal growth were applied for evaluation of the FMIC positive predictive value (PPV) for diagnosis of cases with microcephaly at birth (MICB). Optimal HC cut-offs were determined for each of the new references aimed at detection of all MICB cases and minimizing the number of false positive ones found with a normal head circumference at birth (NHCB). We assessed: the PPV of the FMIC for MICB diagnosis, the difference between the z-scores of the prenatal HC and the corresponding OFC at birth, the frequency of growth restriction, decreased HC/abdominal circumference (AC) and HC/femur length (FL), the percentage of associated malformations, and family history.

RESULTS: Forty two fetuses were diagnosed as having FMIC according to the CR. In only 24 microcephaly was confirmed at birth or by autopsy (PPV 57.1%). The optimal I21P and IR HC cut-offs for MICB diagnosis were the mean-3SD and the mean-2.3SD, resulting in a statistically non-significant PPV improvement of 61.5% and 66.7%, respectively. The presence of family history of MIC, IUGR, associated malformations and application of stricter HC cut-offs resulted in a higher prediction rate of MICB, although not statistically significant. The deviation of the HC from the mean, by all references, was significantly larger compared to the actual deviation of the OFC at birth. The mean differences between the corresponding z-scores of the HC and OFC were -1.15, -1.95, and -0.74 for the CR, I21P, and IR, respectively. The estimated weight of the cases with FMIC was below the 10$^{th}$ and 3$^{rd}$ percentile in 83.3% and 42.9%, correspondingly. A birth weight below the 3$^{rd}$ percentile was found

in 34.8% of MICB and in 11.1% of NHCB ($p<0.05$). A low HC/AC and a low HC/FL were found in 37.5% and 50% of MICB, and 27.8% and 55.6% NHCB cases, respectively. Associated anomalies were found in 58.3% of MICB compared to 27.8% of NHCB.

CONCLUSIONS: The evaluated references, all result in considerable over diagnosis of fetal microcephaly. The use of the two new HC references did not significantly improve MICB prediction compared to Chervenak et al's one. The OFC deviates significantly less from the mean compared to the HC. By addition of a family history, associated anomalies, IUGR, and stricter HC cut-offs we could improve the predictive accuracy. We suggest that addition of the difference between the HC and OFC z-scores, developed in this study, to a particular HC z-score will enable better estimation of the actual OFC deviation at birth.

## Introduction

Microcephaly (MIC) is frequently associated with intellectual disability and neurologic abnormalities. The definition of MIC after birth is non-uniform. Usually it is defined as an occipitofrontal circumference (OFC) more than 2 standard deviations (SD)[1] below the mean for age and gender, but some authors put the OFC cut-off at -3SD[2]. Assuming a normal OFC distribution, 2.3% of children would be defined as microcephalic based on an OFC of 2SD below the mean. However, published estimates for this threshold at birth are lower (0.56%[3] and 0.54%[4]). For an OFC of 3SD below the mean only 0.1% of children would be diagnosed with MIC, which corresponds to the published estimate of 0.14% of neonates[4]. The incidence of intellectual disability correlates with the number of SDs the OFC deviates below the mean: 11% and 51% for 2SD and 3SD, correspondingly[4].

Similarly, the diagnosis of fetal microcephaly (FMIC) also relies on the measurement of an abnormally small fetal head circumference (HC). There are many published nomograms for fetal HC growth. Although new HC references have recently been developed, the established ones are still commonly used, despite being based on relatively small groups of fetuses and outdated measurement modalities [5,6].

The yield of the commonly used growth charts for prenatal MIC diagnosis is considered low. The inaccuracy is primarily related to the inconsistent HC measurement methodology and the absence of properly designed studies aimed at optimization of predictive strategies for prenatal diagnosis of MIC. Furthermore, the sonographic HC z-score (expressed as a number of standard deviations below the mean for gestational age) is consistently over-estimated relative to the corresponding postnatal OFC z-score. In a study of fetuses with HC z-scores between -2 and -3, 90% were found to be normocephalic at birth[7].

In 1984 Jeanty et al developed HC growth standards based on a longitudinal assessment of 45 normal pregnancies of medical personnel volunteers in New Haven, Connecticut[5]. This reference was applied to fetuses with suspected microcephaly in two studies by Chervenak et al[8,9]. The studies included a total of 40 fetuses. In only 13 MIC was confirmed at birth. Their established cut-off for FMIC diagnosis (HC z-score $\leq$ -3SD) was associated with a PPV of 46%[8] and 50%[9] for a false negative rate of zero and 15%, correspondingly. As a result of the low PPV numerous fetuses may

be wrongly diagnosed as microcephalic; and in countries where termination of pregnancy is an option, it may be inadequately offered.

Our study's main goals were to assess the accuracy of the established and new HC nomograms in prediction of microcephaly at birth (MICB) and to assess whether integrating additional parameters can improve prediction.

## Materials and Methods

The records of cases with FMIC diagnosed between 2007 and 2014 were collected from the registries of four Israeli medical centers. The inclusion criteria were: available records of singleton pregnancies with a sonographically documented gestational age in the first or early second trimester, a HC 3SD below the mean for gestational age according to Chervenak et al's reference[8] (CR), OFC and weight at birth or autopsy results.

Examinations were performed with Voluson E8, Voluson 730 Expert, and Voluson 730 Pro (GE Healthcare Ultrasound, Milwaukee, WI, USA) ultrasound machines. All records were evaluated for the medical history, imaging results, laboratory data, and postnatal examination or autopsy findings. Microcephaly was confirmed at birth by an OFC 2SD below the mean[10] or a brain weight of less than 2SD on autopsy[11].

The positive predictive values (PPV) of FMIC for diagnosis of microcephaly at birth were calculated using CR and the two new fetal growth nomograms[12,13].

The new nomograms differed in their methodology. The first, INTERGROWTH-21st Project (I21P), was intended to produce prescriptive fetal growth standards in singleton pregnancies by studying a worldwide cohort of young, educated, affluent, adequately nourished, and clinically healthy women of low risk for adverse pregnancy outcome[12]. The second one was a large Israeli population based reference (IR) of singleton gestations that excluded cases of an uncertain gestational age, fetal malformations, and known fetal syndromes[13]. This reference provided descriptive growth standards without limitations of maternal age and health risk factors. In both new references the HC was measured using an electronic ellipse facility outlining the outer cranial borders, whereas Chervenak et al[8] calculated the HC by using the biparietal diameter (BPD) as an outer-to-inner cranial measurement and the

occipitofrontal diameter (OFD) as a distance between the middle of the bone echoes applying a specific formula: $HC=1.62(BPD+OFD)$[5] (Figure 1).

To keep with the conventional MIC assessment, the z-score method was used for evaluation of the fetal head size. Although originally based on the quantile regression analysis, the IR was adjusted for HC z-score calculation (by developing of HC mean and SD values according to gestational week). The developed table, formulas for the HC and SD, and a HC z-score calculator are provided in the supplementary material.

Optimal HC cut-offs were determined for each HC reference aimed at detection of all MICB cases and minimizing the number of false positive ones found with a normal head circumference at birth (NHCB).

The categorical parameters for integration with HC cut-offs included: associated IUGR (defined as an estimated fetal weight (EFW) below the $10^{th}$ percentile), fetal anomalies, and a family history of MIC.

The biometric parameters were: the EFW calculated according to Hadlock et al[14] (based on BPD, HC, abdominal circumference (AC), and femur length (FL)); fetal and newborn weight percentiles according to Dolberg et al[15]; and HC/AC and HC/FL according to Snijders et al[16].

The accuracy of the HC and integrated criteria for diagnosis of microcephaly at birth were assessed by the PPV and the false negative rate (FNR) for each of the studied references. The PPV was calculated as a number of the MICB cases divided by a number of the MICB and NHCB cases, all fulfilling a specified condition; and the FNR as the number of MICB cases not fulfilling the specified condition divided by all MICB cases. Statistical comparison between the PPV and FNR of the studied criteria was performed by $\chi^2$ test.

The HC z-scores according to the applied references were compared in each study group (FMIC, MICB, and NHCB) by t-test for paired samples.

A comparison between the HC z-scores of the MICB and NHCB groups was performed by t-test for unpaired samples.

In each case the difference between the corresponding HC and OFC z-scores was calculated according to the applied references and correlated to the time interval between FMIC diagnosis and OFC assessment at birth.

The data was analyzed by IBM SPSS statistics software (IBM Corporation Software Group, NY, US).

This study was approved by the Institutional Review Boards.

**Results**

Using Chervenak et al's reference[8] a fetal head circumference 3SD below the mean for gestational age was found in 42 fetuses (FMIC), of them at birth 24 were diagnosed with microcephaly (MICB) and 18 had a normal HC (NHCB). The mean gestational week at FMIC diagnosis was 32.6 ± 5.6 (range: 22 to 38). The mean gestational week did not significantly differ between the MICB and the NHCB subgroups (33.7 ± 5.3 and 31.0 ± 5.7, correspondingly). The female/male ratio of FMIC was 1/1.14. A karyotype was obtained in 27 fetuses and was normal in all. Serology for intrauterine infection was negative in all (including 2 cases of histologically confirmed CMV fetopathy). Associated fetal anomalies were found in 45.2%, 58.3%, and 27.8% of FMIC, MICB, and NHCB cases, correspondingly.

The definite or possible etiology for microcephaly was determined in 23 of 24 MICB cases: primary MIC (3), malformation of cortical development (4), pontocerebellar hypoplasia (2), vermian hypoplasia (1), CMV fetopathy (2), hypoxic/hemorrhagic brain damage (2), fetal alcohol syndrome (1), placental pathology (4), syndromic MIC (3), and Aicardi-Goutières syndrome (1).

The etiology for small HC was established in 16 of 18 NHCB cases: Chiari-II malformation with open spina bifida (4), vertical cranial elongation (5, coronal craniosynostosis (1) and skull molding (4)), and placental pathology (2).

Microcephaly at birth was confirmed in only 24 fetuses according to Chervenak et al[8] (HC below mean-3SD) resulting in PPV of 57.1%. The optimal HC cut-offs for I21P and IR were: mean-3SD and mean-2.3SD, correspondingly. These cut-offs resulted in a PPV of 61.5% and 66.7%, respectively. Application of the 1$^{st}$ quantile cut-off of the IR (the lowest reported quantile in the original paper[13]) provided a PPV of 65.7% with a FNR of 4.2%. The PPV of the optimal HC cut-offs did not differ significantly between the references ($\chi^2$ test).

Table 1 summarizes the accuracy of the applied references for MICB diagnosis using stricter and optimal HC cut-offs with integration of additional parameters (IUGR, fetal malformations, and family history). Both, CR and IR achieved a PPV of 100% for MICB at a HC $\leq$ mean-4SD, whereas I21P did not exceed the PPV of 66.7% even at a HC$\leq$ mean-6SD. Integration of the optimal HC cut-offs with the presence of IUGR, fetal anomalies, or family history had an additive effect on MICB prediction

for all three references. Adding IUGR resulted in a PPV of 62.9%, 66.7%, and 73.3% for EFW below the 10$^{th}$ percentile and 66.7%, 70.6%, and 75% below the 3$^{rd}$ percentile for the CR, I21P, and IR, respectively. Integration of the optimal HC cut-offs with the presence of fetal anomalies resulted in a MICB PPV of 70%, 73.7%, and 82.4% for CR, I21P, and IR, correspondingly. Addition of a family history of MIC resulted in a PPV of 100% for each reference. A comparison between the PPVs of the above mentioned criteria did not reach statistical significance for each of the references (explained by the small size of the groups). Similarly, the PPVs did not differ significantly between the references, tested for the corresponding criteria ($\chi^2$ test). As a rule, stricter HC cut-offs and integrated conditions were associated with a high FNR of MICB for all references, reaching a maximum of 87.5% for the optimal HC cut-off integrated with family history of MIC ($p<0.0001$, compared to a FNR of an optimal HC cut-off alone; $\chi^2$ test).

The mean HC z-scores in FMIC, MICB, and NHCB groups are presented in Table 2. The I21P reference showed significantly lower HC z-scores compared to the other two references, tested in each of the study groups ($p<0.0001$, t-test for paired samples).

When the HC z-scores of the MICB fetuses were evaluated by CR and IR, they were significantly lower compared to the NHCB's ones ($p<0.04$ and $p<0.02$ for CR and IR, correspondingly; t-test for unpaired samples).

The HC z-scores of FMIC, MICB, and NHCB groups were significantly lower ($p<0.005$, paired t-test) than the corresponding OFC ones for all prenatal references, except for the MICB group according to IR (Table 3). The mean differences between the HC and OFC z-scores of FMIC fetuses were: -1.15 (95% CI: -1.51 to -0.79), -1.95 (95% CI: -2.47 to -1.44), and -0.74 (95% CI: -1.07 to -0.40) for CR, I21P, and IR, respectively.

The time interval between FMIC diagnosis and OFC assessment at birth was 2.4±4.1 weeks ranging between 1day and 17.6 weeks. No significant correlation was found between the difference of the corresponding HC and OFC z-scores and the time interval between the two assessments (Pearson's correlation coefficients were -0.05, -0.3, and -0.15 for CR, I21P, and IR, respectively).

The EFW of the FMIC cases was below the 10$^{th}$ and 3$^{rd}$ percentile in 83.3% and 42.9%, respectively. A birth weight below the 10$^{th}$ percentile was found in 78.3% and 33.3% of MICB and NHCB cases, and below the 3$^{rd}$ percentile in 34.8% and 11.1%, correspondingly. A low birth weight was significantly more frequent in MICB cases compared to NHCB ($p<0.05$).

A HC/AC <5$^{th}$ percentile was found in 33.3%, 37.5%, and 27.8% of FMIC, MICB, and NHCB cases; and a HC/FL <5$^{th}$ percentile in 52.4%, 50%, and 55.6%, respectively.

Termination of pregnancy was performed in 20 FMIC cases upon parental request (47.6%): 11 and 9 fetuses of the MICB and NHCB groups, correspondingly. Abnormal CNS finding on autopsy were found in 63.6% of MICB and in 33.3% of NHCB (all with Chiari-II malformation). Six autopsies of fetuses from the NHCB group were anatomically normal.

Neurological abnormalities were reported in 84.6% and 11.1% ($p=0.01$) of MICB and NHCB live births, correspondingly. Death during the first 7 years occurred in 53.8%, and 0% of MICB, and NHCB cases, respectively. Eight of the 9 patients from the NHCB group had normal development.

**Discussion**

In a recent update on a classification of malformations of cortical development by Barkovich et al[17], microcephaly is categorized according to the onset of the disorder relative to the glial and neuronal migration phase. The premigrational category includes multiple genetic disorders that manifest by fetal and neonatal microcephaly due to reduced proliferation or excessive apoptosis of neuronal and glial cells. The post-migrational category is related to decreased brain growth during late gestation or the early postnatal period as a result of ischemia, infection, trauma, inborn metabolic disorders, teratogens, and genetic factors. The last category develops in the first two years of life, however, prenatal diagnosis may be possible, if the deceleration in head growth is progressive and occurs relatively early in the third trimester. Patients with isolated genetic MIC (primary MIC) are almost always born with a significantly small OFC, but are not necessarily considered microcephalic at birth. Syndromic MIC (associated with dysmorphism and/or brain and/or systemic malformations) is usually diagnosed postnatally[18].

FMIC, defined as a HC 3SD below the mean[8], can be expected in 0.1% of pregnancies, if the HC is normally distributed. However, the actual estimate of such low HC measurements is probably higher. According to the Israeli registry[13] of the 11169 singleton pregnancies with certain dating and no fetal anatomical malformations or known syndromes, 23 (0.2%) were found to have FMIC, while only 13 of them were diagnosed as microcephalic postnatally, resulting in a population estimate of a false positive rate of 0.1%.

The correct prediction of MICB based on prenatal biometry is suboptimal[19]. In our series, the established reference[8] resulted in over-diagnosis of FMIC in 43% of cases, leading to erroneous termination of 6 pregnancies with apparently normal fetuses.

The use of the two new HC references[12,13] did not significantly improve MICB prediction compared to Chervenak et al's one[8] (explained by a relatively small series).

The low predictive accuracy can also be related to the nomogram's statistical properties: a mean HC that is too high for the actual population or a SD value that is too small, may cause substantial changes in the z-score calculation. Figure 2 demonstrates that the mean HC growth curves, before 32-33 gestational weeks, are very similar for all three references, whereas the nomogram used in CR[5] shows a

progressive HC increment in later gestational weeks, relative to the I21P and IR. Since 60% of our FMIC cases were diagnosed after 33 weeks, it can partially explain the higher percentage of false positive cases according to CR.

The I21P data showed significantly lower HC z-scores compared to the other references (Table 2) resulted by the low SD values of the I21P nomogram (Figure 2). The extremely deviated HC z-scores were found in 6 NHCB cases (-3.9 to -6.6) and in 4 MICB ones (-4.3 to -6.4), thus explaining why the I21P nomogram did not exceed a PPV of 66.7% even with very strict HC cut-offs (Table 1).

A PPV of 100% was achieved for the HC cut-off below mean-4SD using both the CR and IR nomograms. Adding a family history of MIC to the optimal HC cut-offs also resulted in a PPV of 100% using all three references. Integrating either the presence of IUGR or the association of fetal anomalies with the optimal HC cut-off by the IR gave a maximal PPV of 75% and 82.4%, correspondingly (Table 1). Our series is relatively small due to the rarity of a measurement of a HC$\leq$ mean-3SD. Therefore, the additive prediction of the stricter HC cut-offs and the integration of additional parameters did not reach statistical significance. However, we suggest that considering these parameters in every case of FMIC can improve the accuracy of MICB prediction, although this improvement is associated with significantly high false negative rates using all studied references (Table 1). This indicates that in many FMIC cases the absence of integrated parameters will preclude accurate diagnosis of MICB.

The difference between intrauterine and postnatal measurements of head size prevents accurate MICB prediction (Figure 1). Sonographic HC measurements are consistently underestimated relative to postnatal OFC and the difference increased with gestational age[20]. The probable cause for the discrepancy is that the HC is measured as the perimeter of the fetal skull while the OFC includes the scalp and hair. However, differences in the anatomical landmarks for the HC and OFC assessment, molding, scalp edema, interobserver and intraobserver variability of the HC measurements[21] may also affect the magnitude of the inconsistency. Our study demonstrates that in addition to the multifactorial discrepancy between the HC and OFC measurements, the deviation of the HC from the mean was significantly larger compared to the actual deviation of the OFC at birth for all references (Table 3).

No information exists on the correlation between the severity of FMIC and the risk for intellectual disability; the only established risks are based on the degree of the postnatal OFC deviation[4,22]. Therefore, only achievement of accurate prediction of the OFC z-score at birth will enable precise prenatal prognostication. Based on calculations in our study group we can provide confidence interval limits of the difference between the HC and OFC z-scores (Table 3). These limits can be added to a particular HC z-score in order to predict the range of the OFC one. The accuracy of this new approach should be confirmed in future studies.

FMIC frequently presents with IUGR. In a study on congenital microcephaly detected by prenatal ultrasound, 66% of the MICB cases were small for gestational age[23]. IUGR is described in multiple disorders of both pre- and postmigrational microcephaly[17,21,24]. FMIC in such cases can be misinterpreted as part of general fetal growth restriction without taking into account a small head as an alarming prognostic factor. Our study also confirms that MICB is strongly associated with IUGR, indicating that restricted fetal growth cannot be considered as a "simple" explanation for a small HC. According to our and den Hollander et al's results[23] a normal HC/AC is found in the majority of FMIC cases, thus indicating that a disproportionately small HC is not a typical feature of fetal microcephaly.

Recently a novel statistical approach allowing accurate individualized prediction of late fetal and neonatal growth outcomes was proposed by Deter et al[25,26]. This method is based on serial sonographic assessments of multiple biometric parameters (starting from 18 gestational weeks and continuing all through pregnancy at 3-4 week intervals). Unfortunately such a systematic follow-up is not always available in FMIC cases which are usually first diagnosed in the third trimester. Moreover, the accuracy of this approach for prediction of MICB needs to be assessed.

Placental pathology was an infrequent explanation for the association of MICB and IUGR in our study (16.7%, 4/24). In contrast, Dahlgren et al[27] found that 79% of microcephalic newborns had abnormal placental findings. However, it is not clear if this was the sole pathology or part of a more complex disorder.

Our study showed no significant improvement in predicting MICB by application of the new HC references compared to the established one. By addition of a family history, associated anomalies, IUGR, and stricter HC cut-offs we could improve the

predictive accuracy, however this improvement was not statistically significant due to the small study groups. It is important to realize that in many MIC cases there are no additional parameters to consider and therefore the ability to accurately predict postnatal microcephaly remains limited. We found significantly better OFC z-scores compared to the corresponding HC ones. We suggest that addition of the confidence interval limits of the difference between the HC and OFC z-scores to a particular HC z-score will enable an improved estimation of the actual OFC z-score at birth and more precise counseling in cases with FMIC.

**Study limitations:**

Our study was designed to predict a pathologically small OFC at birth without considering the postnatal clinical outcome. The study was based on a relatively small cohort. The correlation between the degree of fetal HC smallness and the incidence of MIC during the postnatal years was not addressed. The correlation between the severity of FMIC and intellectual disability was not studied.

Table 1. Accuracy of fetal HC cut-offs and integrated parameters in predicting microcephaly at birth according to the applied references

| Predictive criterion | Positive predictive value % (cases[#]) | False negative rate % (cases[†]) |
|---|---|---|
| Chervenak et al[8] | | |
| HC≤mean-3SD | 57.1 (24/42) | NA* |
| HC≤mean-3SD and EFW<10th% | 62.9 (22/35) | 8.3 (2/24) |
| HC≤mean-3SD and EFW<3rd% | 66.7 (12/18) | 50.0 (12/24) |
| HC≤mean-3SD and fetal anomalies | 70.0 (14/20) | 41.7 (10/24) |
| HC≤mean-3SD and familial MIC | 100.0 (3/3) | 87.5 (21/24) |
| HC≤mean-4SD | 100.0 (8/8) | 66.7 (16/24) |
| | | |
| Papageorghiou et al[12] | | |
| HC≤mean-3SD | 61.5 (24/39) | 0.0 (0/24) |
| HC≤mean-3SD and EFW<10th% | 66.7 (22/33) | 8.3 (2/24) |
| HC≤mean-3SD and EFW<3rd% | 70.6 (12/17) | 50.0 (12/24) |
| HC≤mean-3SD and fetal anomalies | 73.7 (14/19) | 41.7 (10/24) |
| HC≤mean-3SD and familial MIC | 100.0 (3/3) | 87.5 (21/24) |
| HC≤mean-4SD | 65.4 (17/26) | 29.2 (7/24) |
| HC≤mean-5SD | 66.7 (8/12) | 66.7 (16/24) |
| HC≤mean-6SD | 66.7 (4/6) | 83.3 (20/24) |
| | | |
| Daniel-Spiegel et al[13] | | |
| HC≤mean-2.3SD | 66.7 (24/36) | 0.0 (0/24) |
| HC≤mean-2.3SD and EFW<10th% | 73.3 (22/30) | 8.3 (2/24) |
| HC≤mean-2.3SD and EFW<3rd% | 75.0 (12/16) | 50.0 (12/24) |
| HC≤mean-2.3SD and fetal anomalies | 82.4 (14/17) | 41.7 (10/24) |
| HC≤mean-2.3SD and familial MIC | 100.0 (3/3) | 87.5 (21/24) |
| HC<1st quantile | 65.7 (23/35) | 4.2 (1/24) |
| HC≤mean-3SD | 71.4 (15/21) | 37.5 (9/24) |
| HC≤mean-4SD | 100.0 (4/4) | 83.3 (20/24) |

HC - head circumference; SD - standard deviation; EFW - estimated fetal weight

* NA - not applicable (this cut-off was the inclusion criterion).

[#] Numbers in parentheses indicate the MICB cases / (MICB+NHCB) cases, all fulfilling the specified condition.

[†] Numbers in parentheses indicate the MICB cases not fulfilling the specified condition / all MICB cases.

Table 2. HC z-scores in the study groups according to the applied references

| Reference | HC z-score FMIC (42 cases) mean (SD) | HC z-score MICB (24 cases) mean (SD) | HC z-score NHCB (18 cases) mean (SD) |
|---|---|---|---|
| Chervenak et al[8] (CR) | -3.56 (0.65) | -3.74 (0.75)[†] | -3.33 (0.37)[†] |
| Papageorghiou et al[12] (I21P) | -4.4 (1.12)[*] | -4.56 (1.03)[*‡] | -4.19 (1.24)[*‡] |
| Daniel-Spiegel et al[13] (IR) | -3.16 (0.9) | -3.45 (0.97)[¶] | -2.78 (0.65)[¶] |

HC - head circumference; SD - standard deviation;

FMIC - fetal microcephaly; MICB - microcephaly at birth; NHCB - normal head circumference at birth.

The HC z-scores of each study group were compared according to the applied references using the t-test for paired samples. The HC z-scores by the I21P were significantly lower compared to ones by the CR and IR ($p<0.0001^{*}$) in all study groups. No statistically significant difference was found comparing the HC z-scores according to the CR and IR in each of the groups.

The HC z-scores of the MICB and NHCB cases were compared by t-test for unpaired samples using each reference. The MICB cases had significantly lower HC z-scores compared to the NHCB's ones using CR and IR ($p<0.04^{\dagger}$ and $p<0.02^{¶}$, correspondingly), while the z-scores did not significantly differ for the I21P ($p=0.3^{‡}$).

Table 3. Difference between the corresponding HC* and OFC† z-scores in the study groups according to the applied references

| Compared references | Z-score difference FMIC (42 cases) mean (SD) | Z-score difference MICB (24 cases) mean (SD) | Z-score difference NHCB (18 cases) mean (SD) |
|---|---|---|---|
| Chervenak et al[8] vs. Fenton et al[10] | -1.15 (1.14)[#] (95% CI: -1.51 to -0.79)[‡] | -0.52 (1.0)[#] | -1.95 (0.75)[#] |
| Papageorghiou et al[12] vs. Fenton et al[10] | -1.95 (1.62)[#] (95% CI: -2.47 to -1.44)[‡] | -1.24 (1.45)[#] | -2.86 (1.37)[#] |
| Daniel-Spiegel et al[13] vs. Fenton et al[10] | -0.74 (1.06)[#] (95% CI: -1.07 to -0.40)[‡] | -0.18 (0.84)[¶] | -1.44 (0.88)[#] |

HC - head circumference; OFC - occipitofrontal circumference; SD - standard deviation; CI - confidence interval; FMIC - fetal microcephaly; MICB - microcephaly at birth; NHCB - normal head circumference at birth.

* Assessed at FMIC diagnosis

† Assessed at birth

‡ 95% confidence intervals of the z-score differences are provided for the suggested estimation of the actual OFC z-score at birth (see Discussion).

The differences between the corresponding HC and OFC z-scores were examined in each study group comparing the z-scores according to the prenatal HC nomograms[8,12,13] and the postnatal OFC reference[10]; (#$p<0.005$, ¶$p=0.31$; paired t-test).

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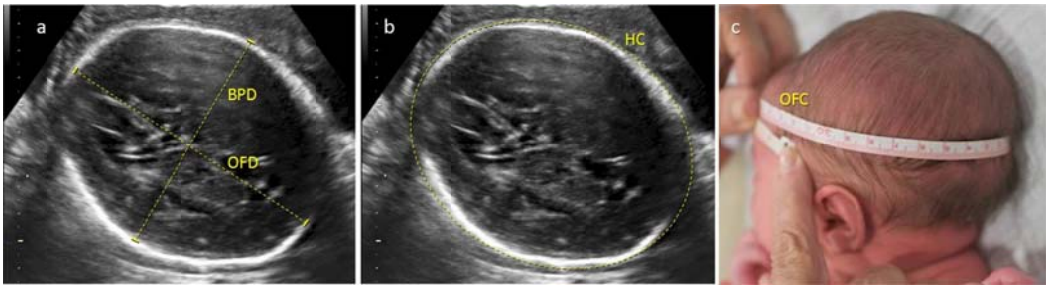


Figure 1. Assessment of fetal head circumference (HC) and neonatal occipitofrontal circumference (OFC)

Legend

Panel (a) demonstrates the method of HC assessment used in Chervenak et al's reference[8] (developed by Jeanty et al[5]). The biparietal diameter (BPD) is measured as an outer-to-inner cranial measurement and the occipitofrontal diameter (OFD) as a distance between the middle of the bone echoes. The head circumference is calculated by a formula: HC=1.62(BPD+OFD).

Panel (b) shows HC measurement using an electronic ellipse facility outlining the outer cranial borders. This method of HC assessment was applied in both new HC references[12,13].

Panel (c) illustrates the postnatal OFC measurement including the scalp and hair.

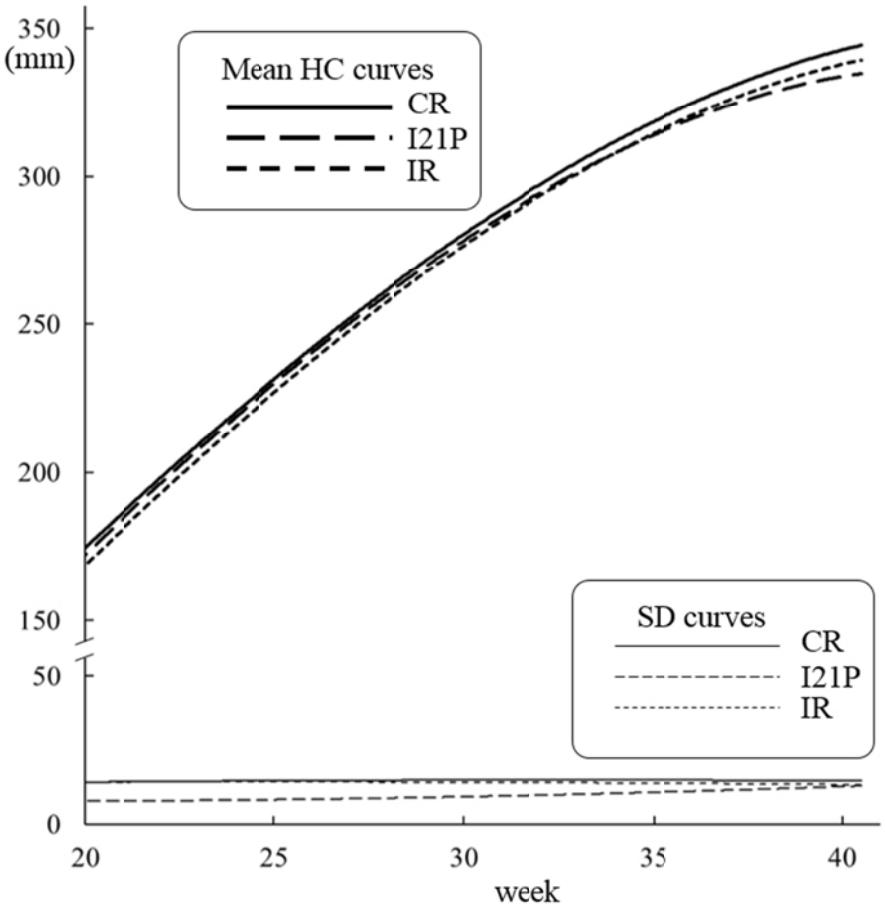


Figure 2. The growth curves of mean head circumference and standard deviation according to the applied references

Legend

CR, Chervenak et al[8]; I21P, Papageorghiou et al[12]; Daniel-Spiegel et al[13].

HC, head circumference; SD, standard deviation.

The curves of the HC and SD of each reference are illustrated according to the indicated line types.