Prenatal gender-customized head circumference nomograms result in reclassification of microcephaly and macrocephaly

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BACKGROUND: Local and worldwide prenatal charts for estimated fetal weight and postnatal charts for head circumference are gender specific. However, prenatal head circumference nomograms are not gender customized.

OBJECTIVE: This study aimed to create gender-customized curves to assess between-gender head circumference differences and to study the clinical significance of using such gender-customized curves.

STUDY DESIGN: A single-center retrospective study was conducted between June 2012 and December 2020. Prenatal head circumference measurements were obtained from routine estimated fetal weight ultrasound scans. Postnatal head circumference measurement at birth and gender were retrieved from computerized neonatal files. Head circumference curves were created, and the normal range was defined for the male and female subpopulations. After applying gender-specific curves, we analyzed the outcome of cases classified as microcephaly and macrocephaly according to non—gender-customized curves, which were reclassified as normal according to gender-specific curves. For these cases, clinical information and postnatal long-term outcomes were retrieved from patients' medical records.

RESULTS: The cohort included 11,404 participants (6000 males and 5404 females). The curve for male head circumference was significantly higher than the female curve for all gestational weeks ($P<.0001$). Applying gender customized curves resulted in fewer cases of male fetuses defined as 2 standard deviations above the normal range and female fetuses defined as 2 standard deviations below of the normal range. Cases reclassified as normal head circumference after the application of gender-customized curves were not related to increased adverse postnatal outcomes. The rate of neurocognitive phenotypes was not higher than the expected rate in both male and female cohorts. Polyhydramnios and gestational diabetes mellitus were more common in the normalized male cohort, whereas oligohydramnios, fetal growth restriction, and cesarean delivery were more common in the normalized female cohort.

CONCLUSION: Prenatal gender-customized curves for head circumference can reduce the overdiagnosis of microcephaly in females and macrocephaly in males. According to our results, gender-customized curves did not affect the clinical yield of prenatal measurements. Therefore, we suggest that gender-specific curves be used to avoid unnecessary workup and parental anxiety.

Key words: curve, head circumference, gender customized

Introduction

Prenatal imaging is aimed at detecting congenital fetal anomalies and other abnormal prenatal findings. The assessment of fetal growth and biometric indices is the basis for screening for fetal, placental, and maternal pathologic conditions. As most growth abnormalities that involve fetal head indices present during the late second and early third trimesters of pregnancy, the World Health Organization (WHO) recommends performing a sonographic assessment of the fetus between 28 and 30 weeks of gestation.

The definition of micro- or macrocephaly is a head circumference (HC) of ≥3 standard deviations (SDs) below or above the mean for a given age and gestational age; however, a cutoff of 2 SDs is frequently used as well.[1−3]

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Why was this study conducted?

Currently, prenatal head circumference (HC) nomograms are not gender customized. This study aimed to create gender-customized curves to assess between-gender HC differences and to analyze the clinical significance of the application of these curves.

Key findings

Gender-customized curves based on a cohort of 6000 males and 5404 females showed that the male HC curve was significantly higher than the female curve for all gestational weeks. Applying gender-customized curves resulted in fewer cases of male fetuses above the normal range and female fetuses below the normal range. Most cases reclassified as normal HC after the application of gender-customized curves were unrelated to an adverse outcome.

What does this add to what is known?

Prenatal gender-customized curves for HC can reduce the overdiagnosis of microcephaly in females and macrocephaly in males without compromising the clinical yield of prenatal measurements.

The etiology of abnormal head indices is highly heterogeneous. Micro- and macrocephaly may be isolated or syndromic, related to ethnic background or environmental factors. Genetic syndromes play an essential role in the etiology of micro- and macrocephaly. An inverse correlation exists between the delta from the appropriate mean and the probability of a genetic diagnosis.[4–7]

During the prenatal period, the diagnosis of micro- or macrocephaly has significant clinical and medicolegal implications. It warrants extensive workup, including additional imaging (targeted sonograms and magnetic resonance imaging [MRI]), serologic testing, and genetic counseling and testing, leading to significant stress for the couples and the caretakers.

The definition of abnormal head indices relies on appropriate HC reference curves. Although postnatal HC nomograms are gender specific with apparent differences between males and females, local- and worldwide-estimated fetal HC charts do not provide gender-specific data.[8–10] A study published in 2004 proposed gender-customized charts based on 2466 females and 2589 males; however, the clinical significance of applying HC gender-customized curves was not addressed.[11] Moreover, gender-specific charts are currently not used in routine clinical prenatal workup.

This study aimed to create gender-specific nomograms for fetal head indices based on a large cohort, explore between-gender differences throughout gestation, and assess the incidence and clinical consequences of reclassification after the application of gender-specific nomograms.

Materials and Methods

A single-center study was conducted at the Helen Schneider Women's Hospital at the Rabin Medical Centre in Israel. Data were retrieved from the computerized medical files between June 2012 and December 2020. The database included HC measurements from 2 datasets: (1) newborns' HC clinical measurement and (2) sonographic fetal HC measurement obtained from low-risk, first-trimester–verified dating scans performed between 24 and 42 weeks of gestation. Fetal biometry measurements were obtained as part of routine second-trimester anatomic scans and in cases where a fetal assessment was performed for various indications, such as obstetrical complications or maternal medical conditions, or as part of a targeted scan for a suspected fetal anomaly. Fetal gender was retrieved from the postnatal dataset.

Statistical analysis

HC curves were constructed using the method described by Royston and Wright.[12] Prenatal and postnatal HC measurements of the entire population and the female and male cohorts were plotted as a function of gestational age. The normal range was defined as <2 SDs above and below the mean. Gender-customized nomograms were created to redefine the normal range for female and male fetuses. All cases where the prenatal HC measurement was performed within 2 weeks before birth were retrieved to assess the correlation between the prenatal and postnatal customized curves. We evaluated the rate of cases outside the normal range according to prenatal and postnatal measurements in the general curves and the gender-customized curve.

The Student t test (2-sided, type 2) was used to measure the differences between the male and female curves. A P value of <.05 was considered statistically significant. Python (version 3.5.1) was used to analyze the data using the following libraries:

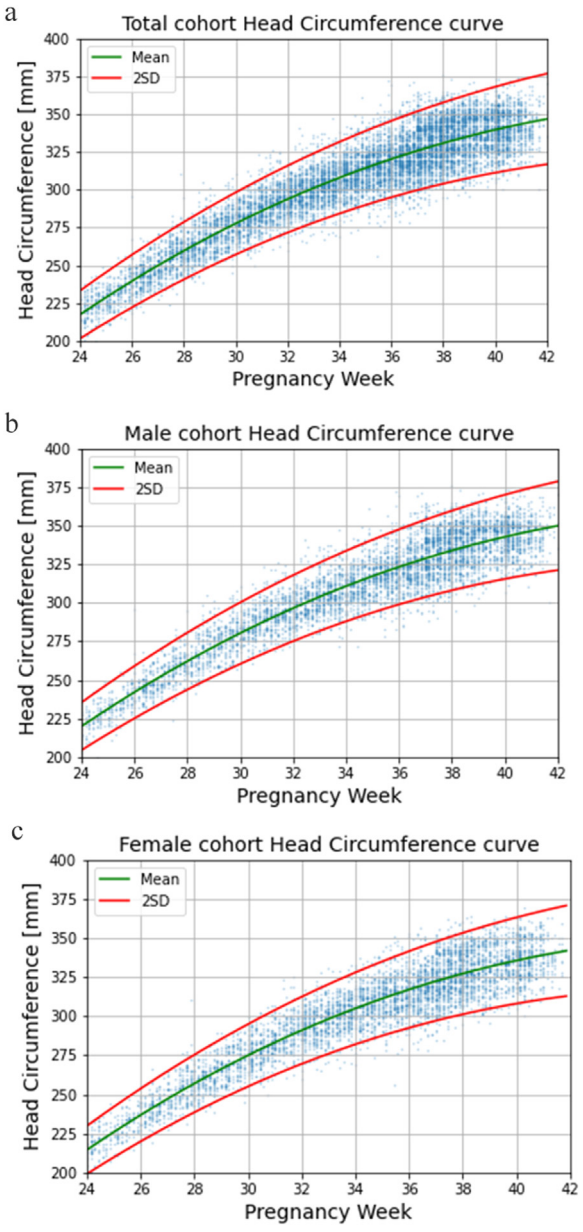
- SCiPy: stats for statistical calculations
- scikit-learn for linear regression

Clinical assessment of the application of gender customized curves. The clinical validity of the new gender-customized fetal HC nomograms was assessed by analyzing the clinical outcome for cases previously categorized prenatally as abnormal and reclassified as normal when applying the gender-customized curves. We assessed 2 cohorts:

1. A cohort of male fetuses with a prenatal measurement of HC classified as above +2 SDs according to non-customized curves and reclassified as normal when applying gender-customized curves
2. A cohort of female fetuses with a prenatal measurement of HC classified as below −2 SDs according to non-customized curves and reclassified as normal when applying gender-customized curves

For these cases, all relevant clinical data were retrieved from the patient's medical records, including prenatally detected malformations and postnatal

FIGURE 1
Fetal HC measurements plotted vs gestational age



HC curve of the prenatal cohort. The normal range is between −2 SDs below the mean and +2 SDs above the mean. **A,** All cases. **B,** Male cases. **C,** Female cases.

HC, head circumference; *SD*, standard deviation.

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medical problems detected after birth by clinical examination or imaging and long-term follow-up and genetic testing. The local institutional ethical committee approved the study.

Results

Our prenatal database included 11,404 fetuses (6000 males and 5404 females). Figure 1 shows the HC measurements plotted vs gestational age for the entire cohort (Figure 1, A), for the male cases (Figure 1, B), and for the female cases (Figure 1, C).

The normal range was defined as ±2 SDs. The normal range was calculated for the entire population of fetuses and the male and female cohorts according to gender-specific curves (Figure 2). The male curve was noticeably above the female curve for all gestational ages. The difference between the male and female curves was statistically significant ($P<.0001$).

Table 1 displays fetal HC charts according to gestational age for the entire cohort. Table 2 displays fetal HC charts according to gestational age for the male cohort. Table 3 displays fetal HC charts according to gestational age for the female cohort. Table 4 displays the percentage of abnormal cases in the prenatal cohort according to the curves derived from the entire cohort and according to the gender-customized curves. Applying prenatal gender-specific curves reduced the rate of males classified as +2 SDs and females classified as −2 SDs compared with the percentage of cases defined by the joint curve.

The postnatal database included 69,895 newborns. For 60,723 cases (31,152 males and 29,571 females), we had complete data regarding gestational age at delivery and gender. The normal range was calculated for the entire postnatal population and the male and female cohorts according to gender-specific curves (Supplementary figure 1).

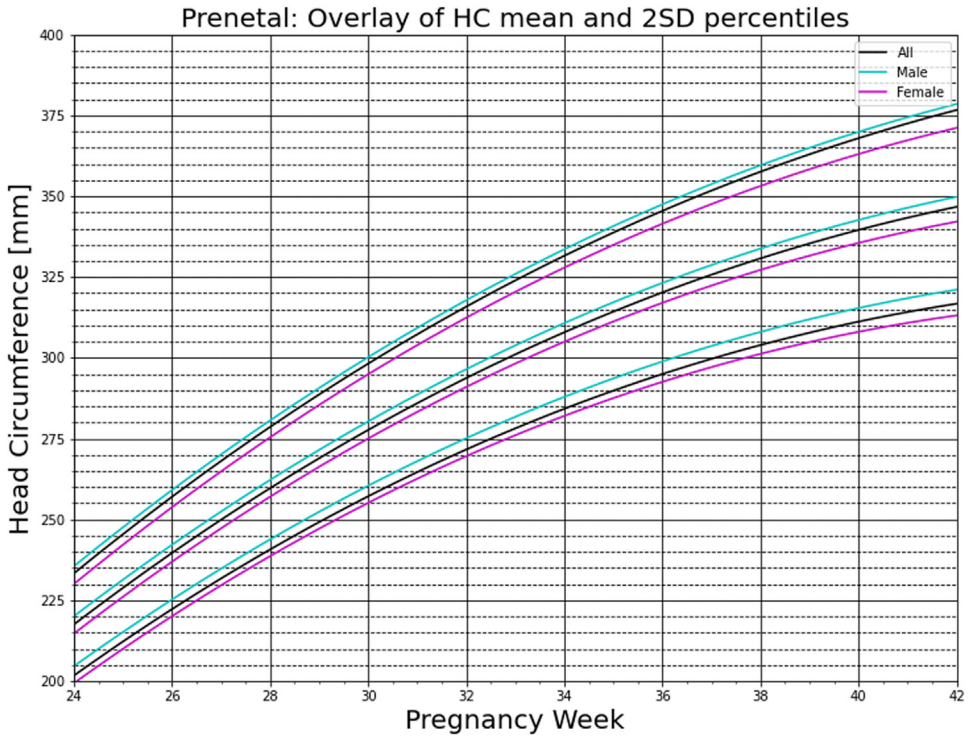
The male HC curve was higher than the female curve for all birth gestational weeks. According to the postnatal gender-specific curves, the HC measurements of 810 males (2.6%) and 790 females (2.67%) were above the normal range, and the HC measurements of 629 males (2.02%) and 619 females (2.09%) were below the normal range.

In 4695 cases (2577 males and 2118 females), prenatal measurements performed 2 weeks before birth were available for analysis. The percentage of males classified as HC above +2 SDs and females classified as HC below −2 SDs was lower when using gender-customized curves for pre- and postnatal HC measurements (Table 5).

To understand the validity of using customized curves, we clinically assessed 2 prenatal cohorts:

1. A cohort of 49 male fetuses with an HC classified as abnormal (above +2

FIGURE 2
The normal range for fetal HC plotted vs gestational age



The figure overlays the normal range for the prenatal curve for the entire population, for female and male cases. The normal range is between −2 SDs below the mean and +2 SDs above the mean.

HC, head circumference; *SD*, standard deviation.

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SDs) according to noncustomized curves and reclassified as normal according to gender-customized curves

2. A cohort of 65 female fetuses with an HC classified as abnormal (below −2 SDs) according to noncustomized curves and reclassified as normal according to gender-customized curves

The clinical information for the cohort of male and female cases reclassified as normal is presented in Supplementary Table 1. The postnatal HC measured at the birth of all reclassified cases was within the normal range. Within the reclassified males, 18 (36.7%) were at the normal upper range, and within the reclassified females, 15 (23.1%) were at the low normal range.

In the normalized male cohort, polyhydramnios and gestational diabetes mellitus (GDM) were more common compared with the normalized female cohort. In 5 cases within the normalized male group, a neurocognitive phenotype was detected postnatally, including 2 cases of speech delay; 1 case of high-functioning autistic spectrum disorder; 1 case of global hypotonia and hyperlaxity, motor delay, and paternally inherited progressive macrocephaly (+3 SDs at the age of 6 years; the father had an HC of +4 SDs), and 1 case of global developmental delay and obesity. For the latter, a genetic workup was performed, and chromosomal microarray testing revealed a 2-Mb deletion at 15q13.1-q13.2 (Chr15:28427485-30497983) (Hg19) inherited from the father categorized as a variant of unknown clinical significance. Whole-exome sequencing (WES) revealed a variant in the *PHIP* gene (NM_017934.5) c.1560C>A, p.Cys520-Ter categorized as likely pathogenic. This variant explained the developmental delay and obesity. The gene is related to the Chung-Jansen syndrome (MIM# 617991).

In the normalized female cohort, oligohydramnios, fetal growth restriction, and cesarean delivery were more common than in the normalized male group. Minor health problems diagnosed after birth were reported in 7 cases. In only one case a significant health problem diagnosed postnatally (Chiari malformation that was not diagnosed prenatally despite anatomic scans).

Of note, 10 cases from the male cohort and 6 cases from the female cohort that were ±3 SDs according to the noncustomized curve were reclassified as normal according to gender-customized curves.

Discussion

Principal findings

This study presented statistically significant differences in fetal HC

TABLE 1
Fetal HC charts according to gestational age for the entire cohort HC

Week	−3 SDs	−2 SDs	−1 SD	Mean	+1 SD	+2 SDs	+3 SDs
24	194	202	210	218	225	233	241
25	204	212	221	229	237	245	254
26	214	222	231	240	248	257	266
27	223	232	241	250	259	268	277
28	231	241	250	260	269	279	288
29	239	249	259	269	279	289	299
30	247	257	267	278	288	298	308
31	254	265	275	286	297	307	318
32	261	272	283	294	305	316	327
33	267	278	290	301	313	324	335
34	272	284	296	308	320	332	343
35	278	290	302	314	327	339	351
36	282	295	308	320	333	345	358
37	287	300	313	326	339	352	365
38	291	304	317	331	344	358	371
39	294	308	322	335	349	363	377
40	297	311	325	340	354	368	382
41	300	314	329	343	358	373	387
42	302	317	332	347	362	377	392

The HC is measured in millimeters.

HC, head circumference; *SD*, standard deviation.

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measurements between genders, with a larger HC in males than in females throughout the second and third trimesters of pregnancy. Applying gender-specific curves resulted in lower rates of male fetuses with an HC above the normal range and female fetuses with an HC below the normal range.

Results

The difference between male- and female-specific growth parameters has been addressed in previous studies.[13−18] Schwärzler et al[11] showed a significant difference in HC between genders and concluded that using sex-specific nomograms may improve the prenatal assessment of fetal growth and provide valuable additional information in high-risk cases. However, the authors did not assess the clinical significance of the utilization of gender-customized curves. In addition, data from local cohorts support gender-specific differences in HC. A study evaluating chromosomal microarray analysis (CMA) in a cohort obtained from the Israeli national health department database revealed a disproportion regarding the gender of prenatally detected microcephaly (87% were females) and macrocephaly (86% were males).[19] This observation was followed by an assessment of the yield of prenatal CMA in cases of microcephaly in a cohort that included 87 prenatal cases and 743 postnatal cases. Among the fetuses who underwent invasive testing for suspected microcephaly, 73.6% were females. In the postnatal group, the distribution between males and females was more balanced and resembled the normal distribution, with only 47.3% microcephalic females (unpublished data, manuscript in preparation).

Therefore, although gender-specific curves for estimated fetal weight and fetal biometry were published, they were not incorporated into routine prenatal practice.[17,18,20] Moreover, non−gender-customized curves are usually used. This might be partly because the clinical significance of applying gender-specific curves was not assessed.

Here, there were several cases with significant adverse outcomes in the male cohort and 1 case of global developmental delay diagnosed with Chung-Jansen syndrome (MIM# 617991). This syndrome is not related to macrocephaly; hence, this diagnosis should be considered an incidental finding. One may argue that the syndrome could have been diagnosed if WES had been performed prenatally because of alleged macrocephaly. However, as HC measured during the pregnancy was only 2 SDs above the normal range (according to the joint curve), the likelihood that WES would have been considered clinically indicated in this case is low.

TABLE 2
Fetal HC charts according to gestational age for the male cohort

Week	−3 SDs	−2 SDs	−1 SD	Mean	+1 SD	+2 SDs	+3 SDs
24	197	205	212	220	228	236	243
25	207	215	223	231	239	248	256
26	217	225	234	242	251	259	268
27	226	235	244	252	261	270	279
28	235	244	253	262	271	281	290
29	243	252	262	272	281	291	300
30	250	260	270	280	290	300	310
31	258	268	278	289	299	309	320
32	264	275	286	296	307	318	329
33	271	282	293	304	315	326	337
34	277	288	299	311	322	334	345
35	282	294	305	317	329	341	353
36	287	299	311	323	335	347	360
37	291	304	316	329	341	354	366
38	295	308	321	334	347	360	372
39	299	312	325	338	352	365	378
40	302	315	329	343	356	370	384
41	304	318	332	346	360	374	388
42	307	321	335	350	364	379	393

The HC is measured in millimeters.

HC, head circumference; *SD*, standard deviation.

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In 1 case of paternally inherited macrocephaly, a genetic workup was not completed; hence, we could not conclude whether this case could have been diagnosed prenatally.

There was 1 case of autism spectrum disorder (ASD) in the male cohort and none in the female cohort (2.0% of the male cohort and 0.9% of the entire cohort). According to the WHO, it is estimated that the worldwide incidence of autism is approximately 1 in 100 children.[21] It is well known that ASD is more prevalent in males; hence, we consider our cohort incidence as not different from the expected rate. Regarding the 2 cases of language delay in the male cohort (4.00% of the male cohort and 1.75% of the entire cohort), the reported rate of language delay among 2-year-old children was as high as 10% to 15%. However, only 4% to 5% remained delayed after 3 years, and this phenotype was also more common in males than females.[22,23] Hence, the incidence of language delay in this reclassified group is not increased. For the female cohort, the proportion of cases with adverse outcomes of reclassified cases was very low (1.5%).

The average birthweight percentile of the normalized male group was significantly higher than in the females (3654 vs 2571 g; $P<.001$), and there was a higher percentage of polyhydramnios, GDM, and large-for-gestational-age (LGA) fetuses. Based on the current data, we may conclude that a relatively large HC, within normal limits according to the gender-specific charts, may be part of an LGA fetus pattern. Similarly, according to the increased incidence of oligohydramnios and small-for-gestational-age fetuses in the female cohort, we may conclude that a relatively small HC, within normal limits according to the gender-specific charts, may be part of an SGA fetus pattern.

Clinical implications

Here, we showed that gender-customized curves lead to a prenatal reclassification of cases considered outside the normal range (0.8% of the male and 1.2% of the female cohorts) without compromising the clinical yield.

When an abnormal HC is detected prenatally, additional workup is required, including genetic counseling, invasive testing (CMA and, in some instances, WES), and further imaging (targeted scans and fetal brain MRI). This may result in parental anxiety, excessive personal and national uptake of resources, and unnecessary testing

TABLE 3
Fetal HC charts according to gestational age for the female cohort

Week	−3 SDs	−2 SDs	−1 SD	Mean	+1 SD	+2 SDs	+3 SDs
24	192	199	207	215	222	230	238
25	202	210	218	226	234	242	250
26	212	220	228	237	245	254	262
27	221	230	238	247	256	265	274
28	229	239	248	257	266	275	285
29	238	247	257	266	276	285	295
30	245	255	265	275	285	295	305
31	252	263	273	283	294	304	314
32	259	270	280	291	302	312	323
33	265	276	287	298	309	320	331
34	271	282	294	305	316	328	339
35	276	288	299	311	323	335	347
36	280	293	305	317	329	341	354
37	285	297	310	322	335	348	360
38	288	301	314	327	340	353	366
39	291	305	318	332	345	358	372
40	294	308	322	336	349	363	377
41	297	311	325	339	353	367	381
42	299	313	328	342	357	371	386

The HC is measured in millimeters.

HC, head circumference; *SD*, standard deviation.

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TABLE 4
Prenatal cohort: cases outside the normal range in the entire cohort and according to gender-customized curves

Variables	Above 2 SDs according to the joint curve	Above 2 SDs according to the male curve	Below 2 SDs according to the joint curve	Below 2 SDs according to the female curve
All cases	283 (2.57)	—	235 (2.13)	—
Males	220 (3.67)	171 (2.85)	53 (0.8)	—
Females	62 (1.15)	—	179 (3.33)	114 (2.11)

Data are presented as number (percentage)

SD, standard deviation.

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and interventions. Parents informed of a diagnosis of fetal malformation experience stress and distress that may have long-term consequences.[24–26] The advantages of reducing unnecessary stress related to prenatal findings and investigation are clear.

Research implications

The data presented in this study suggest the advantage of using gender-customized curves for fetal HC. Further research may shed light on the clinical relevance of gender-customized curves for other fetal biometric parameters, such as long bones, skeleton, and other internal organs.

Large prospective studies with meticulous prenatal neurosonograms, close postnatal neurodevelopmental follow-up, and consideration of parental HC parameters will help establish the

TABLE 5
Correlation between prenatal and postnatal measurements

Variables	All cases	Males	Females
+2 SDs according to non−gender-customized prenatal curves	116 (2.47)	93 (3.61)	23 (1.09)
+2 SDs according to gender-customized prenatal curves	—	72 (2.79)	40 (1.89)
+2 SDs according to non−gender-customized postnatal curves	84 (1.79)	70 (2.72)	14 (0.66)
+2 SDs according to postnatal gender-customized curves	—	51 (1.98)	30 (1.42)
−2 SDs according to non−gender-customized prenatal curves	115 (2.45)	34 (1.32)	81 (3.82)
−2 SDs according to gender-customized prenatal curves	—	71 (2.76)	54 (2.55)
−2 SDs according to non−gender-customized postnatal curves	52 (1.11)	13 (0.50)	39 (1.84)
−2 SDs according to postnatal gender-customized curves	—	31 (1.20)	26 (1.23)

Data are presented as number (percentage).

SD, standard deviation.

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clinical significance of gender-specific differences and the implementation of gender-specific curves.

Strengths and limitations

A key strength of our analysis was that it is based on a large-scale cohort of measurements acquired throughout gestational weeks 24 to 42. This ensured greater precision when estimating percentiles, especially the extreme ends. In addition, meticulous standardization and ongoing auditing of ultrasound measurement protocols ensured consistency and minimized intra- and inter-observer variability. The second strength was the clinical and genetic assessment of reclassified abnormal cases.

The retrospective design of the study may be associated with potential uncontrolled confounders. However, the data for the database was collected prospectively over a 10-year study period and were retrieved from a single center using a consistent standard of ultrasound practice for fetal biometrical measurements. The study only included pregnancies with live-born fetuses as we relied on HC measurements and gender assignment at birth. Another limitation of the study was that multiple pregnancies were excluded as prenatal measurements in this population are more challenging because of uterine crowding. As multiple pregnancies are associated with an increased risk of growth abnormalities, the created nomograms were relevant only for singleton pregnancies.

Conclusions

HC in males was significantly larger than in females throughout gestational weeks 24 to 42, suggesting using gender-customized curves for fetal HC. The reclassification of abnormal cases as normal using gender-specific nomograms was not associated with abnormal clinical outcomes or missed diagnoses and may reduce prenatal workup and parental anxiety. ■

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.xagr.2023.100171.

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