OBSTETRICS

A contemporary amniotic fluid volume chart for the United States: The NICHD Fetal Growth Studies—Singletons

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BACKGROUND: Amniotic fluid is essential to normal fetal development and is estimated clinically with ultrasound scanning to identify pregnancies that are at risk for poor perinatal outcome.

OBJECTIVE: Our goal was to develop a United States standard for amniotic fluid volume that is estimated by the amniotic fluid index and single deepest pocket.

STUDY DESIGN: We performed a planned secondary analysis of a multicenter observational study of 2334 low-risk women with normal singleton gestations from 1 of 4 self-reported racial/ethnic groups. Eligible women had confirmed first-trimester dating criteria with health status, lifestyles, and medical and obstetric histories that were associated with normal fetal growth. Consenting women underwent serial (up to 5) sonographic evaluations of amniotic fluid between 15 and 40 weeks of gestation after being assigned randomly to 1 of 4 gestational age observation schedules. Twelve United States perinatal centers participated, and all sonograms were performed by credentialed sonographers who used identical, high-resolution equipment; caregivers were unaware of results but were notified for oligohydramnios. Women (n=597) who were subsequently found to have clinically significant antepartum complications were excluded. Racial/ethnic–specific nomograms for amniotic fluid index and single deepest pocket across gestation were developed with the use of linear mixed models with cubic splines; racial/ethnic differences were evaluated both with global and between-group tests. Median, 3rd, 5th, 10th, 90th, 95th and 97th percentile values were also estimated. We further considered the possible confounding effects of selected maternal characteristics and the estimated fetal weight at each sonogram.

RESULTS: A total of 1719 pregnant women met inclusion criteria and had available data. These included 480 non-Hispanic white women, 418 non-Hispanic black women, 485 Hispanic women, and 336 Asian women. Both the amniotic fluid index and the single deepest pocket varied across gestation with maximal values at 26 and 33 weeks of gestation, respectively. Statistically significant differences were observed by maternal race/ethnicity. The between-group differences that were observed at 17–22 and 35–40 weeks of gestation remained statistically significant after adjustment for maternal characteristics and estimated fetal weight. These between-group racial/ethnic differences were most prominent after 35 weeks of gestation and at the extremes of dispersion (3rd and 97th percentiles). All 3rd and 97th percentile amniotic fluid index values were within the range of commonly used cutoffs to define oligohydramnios (≤5 cm) and polyhydramnios (≥25 cm). However, the 3rd percentile values ranged between 5.9 cm at 40 weeks of gestation and 10.1 cm at 25–27 weeks of gestation; the 97th percentile values ranged between 24.8 cm at 38 weeks of gestation and 15.7 cm at 15 weeks of gestation.

CONCLUSION: Sonographic amniotic fluid volume estimates vary by racial/ethnic group, but the absolute differences appear to be small and may not be clinically significant. Selected maternal characteristics and estimated fetal weight did not affect the racial/ethnic differences. Between-group differences are maximal after 35 weeks of gestation and at the extremes of the upper and lower dispersion estimates. Given the observed variability in extreme (3rd and 97th percentile) dispersion values over the gestation, use of single cutoffs to define out-of-range measurements may not be appropriate clinically. These data might form a contemporary United States standard for amniotic fluid estimation that uses the amniotic fluid index and the single deepest pocket.

Key words: amniotic fluid index, estimated fetal weight, ethnic, fetal growth, low-risk, racial, single deepest pocket

Amniotic fluid is essential to normal fetal development, particularly the pulmonary and musculoskeletal systems; it also provides umbilical cord protection.[1] Because amniotic fluid volume (AFV) abnormalities are associated with perinatal disease, estimation of AFV is a standard part of obstetric sonography.[2] As an indicator of fetal well-being, it is used commonly as a part of antepartum fetal surveillance as a component of both the modified and complete biophysical profile.[3] It is also used in the evaluation of pregnancies for complications such a premature membrane rupture, twin-twin transfusion syndrome, and fetal congenital anomalies. Well-established methods for the estimation of AFV include the 4-quadrant amniotic fluid index (AFI) and the single deepest pocket (SDP), both are reproducible semiquantitative techniques, although the visual subjective estimate of an experienced sonographer has also been used.[2]

To date there has been no published sonographic AFV standard for women in the United States. Previously published nomograms of sonographically estimated AFV across gestation[4–15] have been limited by retrospective, cross-sectional design or uneven representation of measurements across

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AJOG at a Glance

Why was this study conducted?

This study was conducted to develop a United States standard for sonographic estimation of amniotic fluid volume with the use of the the amniotic fluid index and single deepest pocket.

Key findings

A total of 1719 low-risk women from 4 self-reported racial/ethnic groups and with normal pregnancy outcomes underwent serial assessments of amniotic fluid from 15−40 weeks of gestation as part of an National Institute of Child Health and Human Development−funded, multicenter prospective observational study. Small, but statistically significant, racial/ethnic differences were identified. After we controlled for selected maternal characteristics and estimated fetal weight, these racial/ethnic differences persisted, but may not be clinically relevant.

What does this add to what is known?

Compared with previously developed amniotic fluid−gestational age nomograms, these data represent significant improvements in multiple aspects of study design and execution and could represent a legitimate United States standard.

gestation,[4,10,14,15] small sample size that affects precision, especially of dispersion estimates,[5,11,14] and study populations that are not representative of the current diverse US population.[5−8,11−13] Essentially, all nomograms were developed from sonographers who were aware of women's clinical status, although indications for the examinations may not have been specifically for AFV estimation; both are factors that could bias the observations. Most reports also lacked simultaneous estimates of both AFI and SDP, which prevents a comparison of these 2 techniques, especially at the extremes of fluid volumes. Moreover, although ultrasound technology has improved markedly in the past 2 decades, there have been few recent evaluations of AFV across gestation. The possible confounding effects of selected maternal characteristics and estimated fetal size on AFV measurements have also not been well-studied[16−19] and not included in the development of essentially all published studies.[4−15] Finally, current nomograms were not developed from populations that were selected to have maternal characteristics that are associated with normal fetal growth and, reasonably, amniotic fluid production.

Our primary goal was to develop standard AFI and SDP charts for US women and to assess the association of race/ethnicity with these values, while also estimating the association of other maternal characteristics and fetal weight.

Materials and Methods

This is a planned secondary analysis of the National Institute of Child Health and Human Development Fetal Growth Studies−Singletons, a large-scale, multicenter prospective observational cohort study the primary goal of which was to develop US racial/ethnic standards for fetal growth from 10−41 weeks of gestation.[20] Investigators at the 12 clinical sites enrolled 2334 pregnant women between July 2009 and January 2013 from 4 self-reported racial/ethnic groups with optimal characteristics for normal fetal growth. These characteristics included maternal age 18-40 years, body mass index 19−29.9 kg/m^2, and normal obstetric and medical histories. Human subjects' approval was obtained from all clinical sites, and women gave informed consent before data collection. After enrollment, only women with an uncomplicated pregnancies were retained and analyzed for the growth standard and also for this analysis (N=1737). Additional specific details about inclusion and exclusion criteria are detailed in the primary report of the parent study[20] along with a complete description of the cohort's design and methods.[21]

Before consent, all participants underwent a first-trimester ultrasound scan that confirmed a certain last menstrual period date. The ultrasound estimate of gestation had to be between 8+0 and 13+6 weeks of gestation and also match the last menstrual period−based gestational age within 5 days for women between 8+0 and 10+6 weeks of gestation, within 6 days for those between 11+0 and 12+6 weeks of gestation and within 7 days for participants between 13+0 and 13+6 weeks of gestation for continued participation in the study. With these criteria satisfied, the project gestational age was based on the menstrual date. Women were then assigned at random to 1 of 4 sonography schedules (Table 1) to ensure that data were available at each (±1) week gestation without subjecting women to weekly obstetric ultrasound scans between 16 and 26 weeks of gestation and at each week of gestation starting at 28 weeks.

TABLE 1
Sonography schedule

Group	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
A	16	24	30	34	38
B	18	26	31	35	39
C	20	28	32	36	40
D	22	29	33	37	41

Table values indicate the weeks of gestation when the 5 second and third trimester protocol sonograms were to be scheduled, based on participants' randomly assigned groups A-D sonography schedules.

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Sonology

At each study sonogram, credentialed sonographers measured standard fetal biometrics that are used for the fetal

TABLE 2
Selected characteristics among racial/ethnic groups of the National Institute of Child Health and Human Development Fetal Growth Study

Variable	Non-Hispanic white (n=480)	Non-Hispanic black (n=418)	Hispanic (n=485)	Asian and Pacific Islander (n=336)	All (N=1719)	*P* value
Maternal age, y[a]	30.3±4.3	25.5±5.4	27.0±5.4	30.5±4.4	28.2±5.4	<.0001
Height, cm[a,b]	165.7±7.1	164.4±6.8	160.1±6.2	160.5±6.0	162.8±7.0	<.0001
Weight, kg[a,b,c]	63.5±9.0	64.8±9.8	62.2±9.1	57.0±8.2	62.2±9.5	<.0001
Prepregnancy body mass index, kg/m^2[a,b,c,d]	23.1±2.8	23.9±3.2	24.3±3.0	22.2±2.6	23.5±3.0	<.0001
Parity, n (%)						<.0001
0	257 (53.5)	205 (49.0)	188 (38.8)	173 (51.5)	823 (47.9)	
1	162 (33.8)	135 (32.3)	185 (38.1)	130 (38.7)	612 (35.6)	
≥2	61 (12.7)	78 (18.7)	112 (23.1)	33 (9.8)	284 (16.5)	
Infant sex, n (%)						.5691
Male	260 (54.2)	210 (50.2)	243 (50.1)	174 (51.8)	887 (51.6)	
Female	220 (45.8)	208 (49.8)	242 (49.9)	162 (48.2)	832 (48.4)	
Gestational age at initial amniotic fluid volume assessment, wk[a]	20.1±2.7	20.4±3.5	20.6±3.4	20.9±3.2	20.5±3.2	.0042
Gestational age at final amniotic fluid volume assessment, wk[a]	37.5±2.0	37.0±2.5	37.1±2.5	36.8±3.2	37.2±2.5	<.0001
Gestational age at delivery, wk[a]	39.6±1.0	39.5±1.0	39.6±1.0	39.5±1.1	39.5±1.0	.0731
Marital status, n (%)[c]						<.0001
Not married	28 (5.8)	215 (51.6)	131 (27.0)	29 (8.6)	403 (23.5)	
Married or living with partner	451 (94.2)	202 (48.4)	354 (73.0)	307 (91.4)	1314 (76.5)	
Education, n (%)						<.0001
Less than high school	4 (0.8)	46 (11.0)	106 (21.9)	18 (5.4)	174 (10.1)	
High school/equivalent	22 (4.6)	118 (28.2)	113 (23.3)	40 (11.9)	293 (17.0)	
Some college/associate	88 (18.3)	151 (36.1)	181 (37.3)	66 (19.6)	486 (28.3)	
Bachelors' degree	203 (42.3)	65 (15.6)	67 (13.8)	103 (30.7)	438 (25.5)	
Postgraduate degree	163 (34.0)	38 (9.1)	18 (3.7)	109 (32.4)	328 (19.1)	
Family income, n (%)[c]						<.0001
<$30,000	17 (3.7)	175 (48.2)	156 (38.8)	42 (16.5)	390 (26.3)	
$30,000–$39,999	14 (3.0)	25 (6.9)	67 (16.7)	16 (6.3)	122 (8.2)	
$40,000–$49,999	16 (3.5)	45 (12.4)	41 (10.2)	16 (6.3)	118 (8.0)	
$50,000–$74,999	59 (12.7)	33 (9.1)	55 (13.7)	32 (12.6)	179 (12.1)	
$75,000–$99,999	88 (19.0)	38 (10.5)	30 (7.5)	53 (20.9)	209 (14.1)	
≥$100,000	269 (58.1)	47 (12.9)	53 (13.2)	95 (37.4)	464 (31.3)	
Insurance, n (%)						<.0001
Other	26 (5.4)	205 (49.0)	293 (60.4)	52 (15.5)	576 (33.5)	
Private or managed care	454 (94.6)	213 (51.0)	192 (39.6)	284 (84.5)	1143 (66.5)	

Owen et al. US amniotic fluid volume chart. Am J Obstet Gynecol 2019. *(continued)*

growth standard and also measured the AFV using both the 4-quadrant AFI[22] and the SDP techniques[23] with the use of Voluson E8 machines (GE Healthcare, Milwaukee, WI) and multifrequency curvilinear transducers (real-time abdominal 4-8 MHz). Because AFV measurements began at <20 weeks of gestation, the sonographers were trained

TABLE 2
Selected characteristics among racial/ethnic groups of the National Institute of Child Health and Human Development Fetal Growth Study *(continued)*

Variable	Non-Hispanic white (n=480)	Non-Hispanic black (n=418)	Hispanic (n=485)	Asian and Pacific Islander (n=336)	All (N=1719)	*P* value
Full-time employment/student status, n (%)[c]						<.0001
No	82 (17.1)	104 (24.9)	188 (38.8)	114 (33.9)	488 (28.4)	
Yes	398 (82.9)	314 (75.1)	297 (61.2)	222 (66.1)	1231 (71.6)	

[a] Data are given as mean±standard deviation; [b] Prepregnancy, self-reported; [c] Not included in the totals are missing data: weight (n=4), body mass index (n=15), gestational age at final amniotic fluid volume (n=1), marital status (n=2), income (n=237; 17 from non-Hispanic white, 55 from non-Hispanic black, 83 from Hispanic, 82 from Asian and Pacific Islander); [d] Based on self-reported height and weight.

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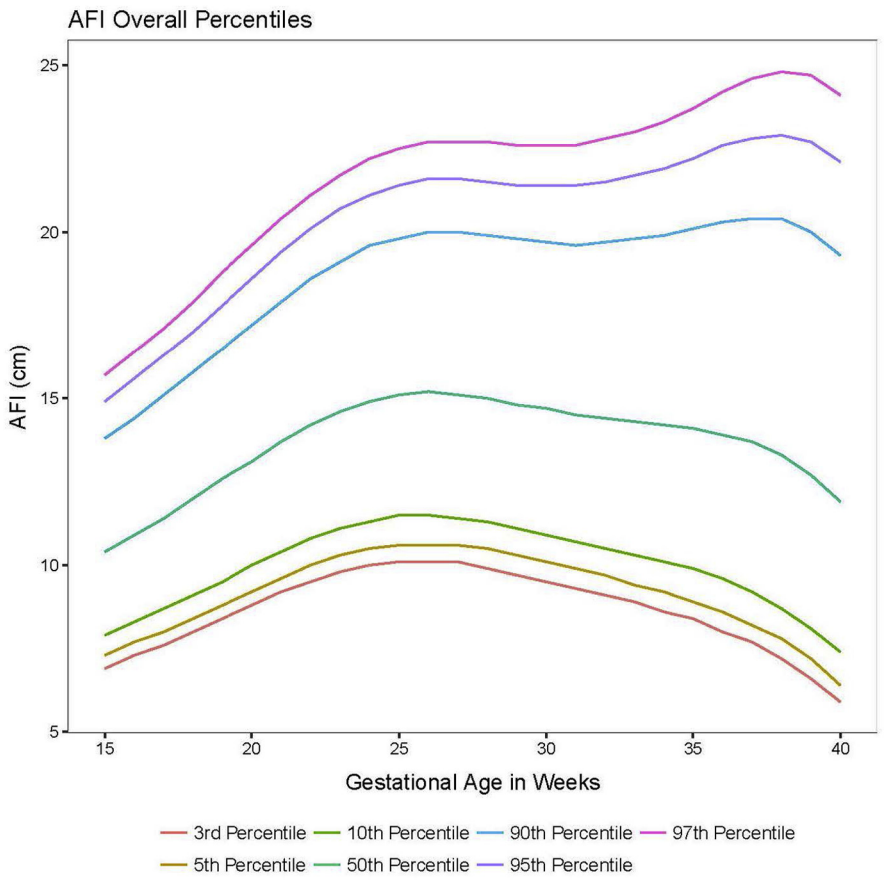
to divide the uterus into 4 quadrants along the sagittal plane and a point halfway to the fundus.[10] The face of the ultrasound transducer was aligned parallel to the floor with the patient supine. Additional fetal biometric measurements were obtained, and estimated fetal weight (EFW) was calculated with the use of the measured fetal head circumference, abdominal circumference, and femoral length with a Hadlock formula.[24]

All study protocol examinations were performed independent of any clinically indicated scans, which also may have been performed per usual clinical practice by the managing physicians. Findings from the study protocol examinations were revealed to managing physicians in cases of severe oligohydramnios, defined as a SDP<2 cm or an AFI<5 cm. All images and measurement data were captured in Viewpoint (GE Healthcare) and electronically transferred to the data coordinating center. Before and during the trial, ultrasound quality was assessed by ante hoc training and credentialing of all site sonographers and a protocol for post hoc quality assurance that included a central review of a random sample of all scans.[25]

FIGURE 1
Unadjusted amniotic fluid index values and percentiles by weeks of gestation (combined race/ethnicities)



Unadjusted AFI median and percentile distribution curves were developed from serial evaluations in 1719 low-risk women enrolled in the National Fetal Growth Studies-Singletons.

AFI, amniotic fluid index.

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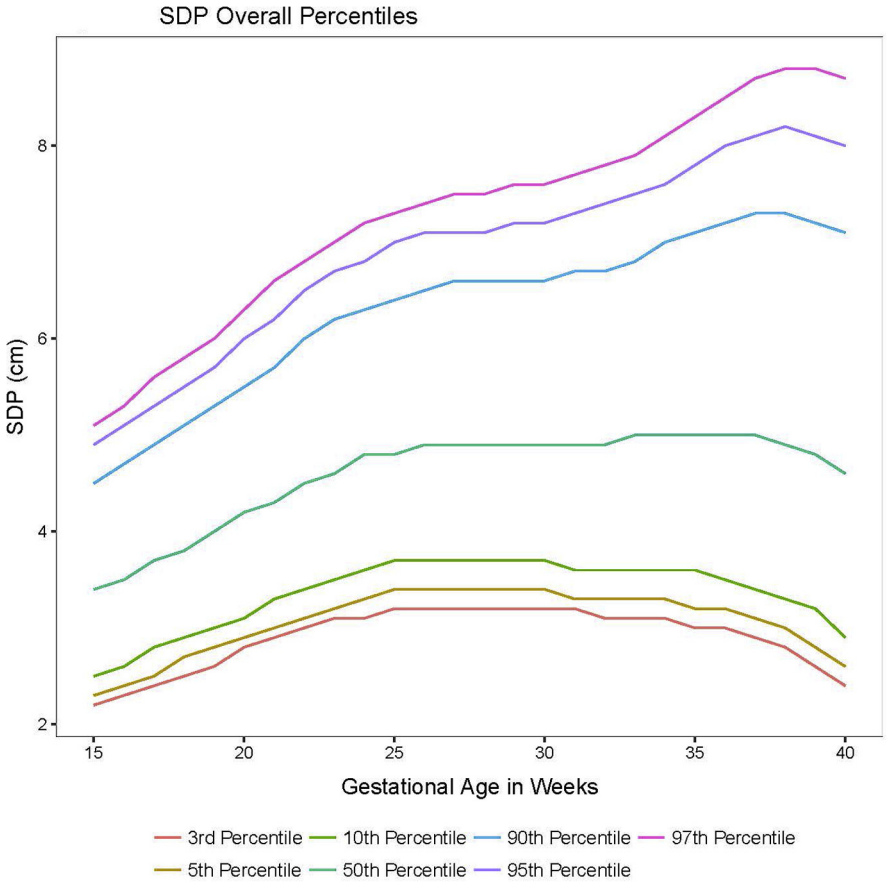
Statistics

Baseline and clinical data were compared for participants by women's self-reported race/ethnicity with the use of chi-square test or *t*-tests for categoric and continuous data, respectively.

AFI and SDP percentiles (3rd, 5th, 10th, median, 90th, 95th, and 97th) were estimated with the use of linear mixed models with cubic splines as fixed effects and cubic terms as random effects corresponding to gestational age. Cubic splines were used to provide a very flexible representation of the trajectories of AFI and SDP across gestational age.[26]

FIGURE 2
Unadjusted single deepest pocket values by weeks of gestation (combined race/ethnicities)



Unadjusted SDP median and percentile distribution curves were developed from serial evaluations in 1719 low-risk women enrolled in the National Fetal Growth Studies-Singletons.

SDP, single deepest pocket.

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Three knot points were chosen for the cubic splines at gestational ages that evenly split the distributions (25th, 50th and 75th percentiles). We a priori chose the knots at the 3 quartile cut points based on each biomarker distribution, because this yields an equal number of measurements within each region separated by the knot points. We chose 3 cut points because our experience has suggested that the underlying trajectories were rather smooth over gestational age and choosing a larger number of knots resulted in unstable trajectories.

Both AFI and SDP values were log-transformed to stabilize variances across gestational age and to improve normal approximations for the error structures. Percentiles were estimated based on the assumed normal distribution of the random effects and error structure. Estimated percentile AFI and SDP curves were first developed across gestation from 15−40 weeks of gestation for the entire population.

Because of the statistically significant racial/ethnic differences in fetal growth that were observed in the entire study population,[20] we next evaluated whether AFI and SDP differed by maternal race/ethnicity (4 groups). We further controlled for the effects of selected maternal characteristics and finally considered the potential effect of the log-transformed EFW at each examination. Selected maternal covariates were assessed as a group and included age, height, weight, parity, full time employment vs student status, marital status (married/living as married vs not), insurance (private, managed vs Medicaid vs other), income, education, and infant sex (male vs female). Annual income and education were analyzed categorically: income $<$\$30,000; \$30,000−\$39,999; \$40,000−\$49,999; \$50,000−\$74,999; \$75,000−\$99,999; $\geq$\$100,000; education: less than high school, high school or equivalent, some college or associate degree, bachelor degree vs master's or higher degree.

Differences among the race/ethnicity groups were evaluated with a global test (ie, likelihood-ratio test) that examined whether there were any differences in the longitudinal mean fluid volume profiles across the 4 groups. These tests were conducted separately for AFI and SDP, for which the global probability value was used to identify any statistically significant differences with the threshold of $<$.05. If the global probability value was found to be statistically significant, we further identified gestational-age-week−specific differences using Wald tests, which compared differences among race/ethnic groups at each week of gestation. The Wald tests were first conducted by a comparison of means across all 4 groups and then by the formation of pairwise tests to compare differences between the racial/ethnic groups at each week of gestation.

All analyses were done with and without collective covariate adjustments (covariates listed previously). We used multiple imputations to account for missing covariate information.[27] We empirically assessed model validity using simulation analysis to ensure unbiased percentile estimates and compared different mixed model cubic splines, cubic polynomials, second-order fractional polynomials, individual-specific interpolation, and smoothing methods.[28,29] All analyses were implemented with the use of SAS software (version 9.4; SAS Institute, Inc, Cary, NC) or R (version 3.1.2; http://www.R-project.org).

TABLE 3
Unadjusted population percentiles for amniotic fluid index by gestational age in normal pregnancies

Gestational age, wk	Percentile							Scans, n
	3rd	5th	10th	50th	90th	95th	97th	
15	6.9	7.3	7.9	10.4	13.8	14.9	15.7	66
16	7.3	7.7	8.3	10.9	14.4	15.6	16.4	113
17	7.6	8.0	8.7	11.4	15.1	16.3	17.1	177
18	8.0	8.4	9.1	12.0	15.8	17.0	17.9	222
19	8.4	8.8	9.5	12.6	16.5	17.8	18.8	228
20	8.8	9.2	10.0	13.1	17.2	18.6	19.6	218
21	9.2	9.6	10.4	13.7	17.9	19.4	20.4	219
22	9.5	10.0	10.8	14.2	18.6	20.1	21.1	207
23	9.8	10.3	11.1	14.6	19.1	20.7	21.7	170
24	10.0	10.5	11.3	14.9	19.6	21.1	22.2	207
25	10.1	10.6	11.5	15.1	19.8	21.4	22.5	201
26	10.1	10.6	11.5	15.2	20.0	21.6	22.7	218
27	10.1	10.6	11.4	15.1	20.0	21.6	22.7	227
28	9.9	10.5	11.3	15.0	19.9	21.5	22.7	379
29	9.7	10.3	11.1	14.8	19.8	21.4	22.6	353
30	9.5	10.1	10.9	14.7	19.7	21.4	22.6	388
31	9.3	9.9	10.7	14.5	19.6	21.4	22.6	347
32	9.1	9.7	10.5	14.4	19.7	21.5	22.8	356
33	8.9	9.4	10.3	14.3	19.8	21.7	23.0	407
34	8.6	9.2	10.1	14.2	19.9	21.9	23.3	385
35	8.4	8.9	9.9	14.1	20.1	22.2	23.7	423
36	8.0	8.6	9.6	13.9	20.3	22.6	24.2	435
37	7.7	8.2	9.2	13.7	20.4	22.8	24.6	431
38	7.2	7.8	8.7	13.3	20.4	22.9	24.8	421
39	6.6	7.2	8.1	12.7	20.0	22.7	24.7	315
40	5.9	6.4	7.4	11.9	19.3	22.1	24.1	61

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Results

Because of missing AFV data, 1719 of the 1737 pregnancies (99.6%) that were included in the fetal growth standard[20] were included in the AFV standard analyses. The final study population included 480 non-Hispanic white (NHW) women, 418 non-Hispanic black (NHB) women, 485 Hispanic women, and 336 Asian women. Maternal characteristics are shown in Table 2. Asian women had the highest mean maternal age, and Hispanic women had the highest prepregnancy body mass index and the highest rate of multiparity. The observed differences in gestational ages at the initial and final ultrasound scans, although statistically significant, were not clinically important. Notably, birth gestational ages were similar across the 4 groups. Marital status, family income, medical insurance, and employment showed significant intergroup differences with NHW women who have the highest rates of marriage, college education, high income, private insurance, and full-time employment in comparison with other racial/ethnic groups of mothers.

Unadjusted overall population AFI and SDP standard nomograms by gestational week are shown in Figures 1 and 2, respectively. Median AFI increased from 15 weeks of gestation, peaked at 26 weeks of gestation, and then underwent a slight but steady decrease through 40 weeks of gestation. In contrast, median SDP steadily increased

TABLE 4
Unadjusted population percentiles for single deepest pocket by gestational age in normal pregnancies

Gestational age, wk	Percentile							Scans, n
	3rd	5th	10th	50th	90th	95th	97th	
15	2.2	2.3	2.5	3.4	4.5	4.9	5.1	66
16	2.3	2.4	2.6	3.5	4.7	5.1	5.3	113
17	2.4	2.5	2.8	3.7	4.9	5.3	5.6	177
18	2.5	2.7	2.9	3.8	5.1	5.5	5.8	222
19	2.6	2.8	3.0	4.0	5.3	5.7	6.0	228
20	2.8	2.9	3.1	4.2	5.5	6.0	6.3	218
21	2.9	3.0	3.3	4.3	5.7	6.2	6.6	219
22	3.0	3.1	3.4	4.5	6.0	6.5	6.8	207
23	3.1	3.2	3.5	4.6	6.2	6.7	7.0	170
24	3.1	3.3	3.6	4.8	6.3	6.8	7.2	207
25	3.2	3.4	3.7	4.8	6.4	7.0	7.3	201
26	3.2	3.4	3.7	4.9	6.5	7.1	7.4	218
27	3.2	3.4	3.7	4.9	6.6	7.1	7.5	227
28	3.2	3.4	3.7	4.9	6.6	7.1	7.5	379
29	3.2	3.4	3.7	4.9	6.6	7.2	7.6	353
30	3.2	3.4	3.7	4.9	6.6	7.2	7.6	388
31	3.2	3.3	3.6	4.9	6.7	7.3	7.7	347
32	3.1	3.3	3.6	4.9	6.7	7.4	7.8	356
33	3.1	3.3	3.6	5.0	6.8	7.5	7.9	407
34	3.1	3.3	3.6	5.0	7.0	7.6	8.1	385
35	3.0	3.2	3.6	5.0	7.1	7.8	8.3	423
36	3.0	3.2	3.5	5.0	7.2	8.0	8.5	435
37	2.9	3.1	3.4	5.0	7.3	8.1	8.7	431
38	2.8	3.0	3.3	4.9	7.3	8.2	8.8	421
39	2.6	2.8	3.2	4.8	7.2	8.1	8.8	315
40	2.4	2.6	2.9	4.6	7.1	8.0	8.7	61

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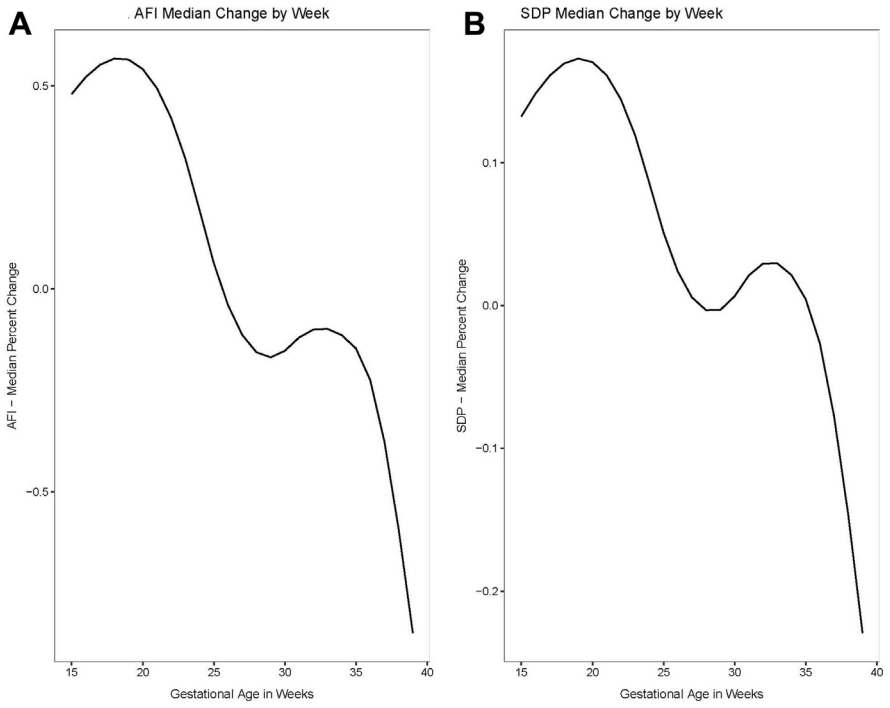
until 33 weeks of gestation and remained relatively constant from 33–37 weeks of gestation, after which there was a slight decline. Unadjusted overall population median and percentile AFI and SDP values by gestational week are presented in Tables 3 and 4, respectively. We confirmed that the variances did not vary by gestational age on the log-transformed scale that we used.[30] Further, our percentiles explicitly accounted for the estimation done in the random effects models by increasing the variability accordingly.

Figure 3 is a graph that depicts the relative magnitude of median AFI and SDP weekly changes throughout gestation from 15–40 weeks of gestation, as estimated by the weekly percent change. Note that small percent changes (near zero on the Y-axis) might not be obviously reflected in Tables 3 and 4 because of rounding. For AFI, median values increased at an accelerated rate until approximately 17 weeks of gestation when the weekly increase began to slow and level off at approximately 26 weeks of gestation, marking its peak. After this time, median AFI began to decrease slowly with a more pronounced decrease beginning at approximately 35 weeks of gestation. Compared with AFI, changes in the SDP demonstrated a similar overall pattern, but with a delayed timing of the changes. For example, the AFI percent change reached zero at 26 weeks of gestation compared with the initial SDP zero change at 27 weeks of gestation. However, the SDP underwent another slight increase from 27–33 weeks of gestation, with a second stable peak from 33–37 weeks of gestation.

FIGURE 3
Percent weekly change in amniotic fluid index and single deepest pocket values



Week-by week change in sonographically measured median AFI (A) and SDP (B) expressed as a percentage.

AFI, amniotic fluid index; *SDP*, single deepest pocket.

Owen et al. US amniotic fluid volume chart. Am J Obstet Gynecol 2019.

As shown in Table 3, the 5th percentile for AFI was >7 cm until 40 weeks of gestation, when it fell to 6.4 cm. The 95th percentile for AFI was always <23 cm, and it stayed at 21−22 cm for 11 weeks of gestation from 24−34 weeks of gestation. When we assessed the most extreme values for AFI, the 3rd percentile remained ≥6 through 39 weeks of gestation and fell to 5.9 cm at 40 weeks of gestation. Conversely, the 97th percentile AFI values increased over gestation and attained values of 24.7 cm at 39 weeks of gestation and 24.1 cm at 40 weeks of gestation. Depicted in Table 4, the 3rd percentile for SDP was at least 2 cm for every gestational week studied. The 97th percentile for SDP increased from 5.1 cm at 15 weeks of gestation to 8.8 cm at 39 weeks of gestation; at 40 weeks of gestation, it fell slightly to 8.7 cm.

Median AFI curves (Figure 4) differed by race/ethnicity (global $P<.001$), with week-specific differences at 17−22 weeks of gestation and 35−40 weeks of gestation (all $P<.05$) that remained significant after adjustment for maternal characteristics and EFW (all Wald $P<.05$). Similarly, as depicted in Figure 5, race/ethnicity affected SDP (global $P<.001$), with week-specific differences at 16−21 weeks of gestation and 36−40 weeks of gestation (all Wald $P< .05$). Although statistically significant inter-racial/ethnic differences were observed, the absolute median differences were generally very small. For example, in the 35-40 week range, the greatest difference was observed at 40 weeks of gestation at which time the NHW women had the largest (13.4 cm) and NHB women the smallest (11.9 cm) unadjusted median AFI values; however, the absolute difference was only 1.5 cm. In the 17−22 week range, the maximum differences among the cohorts were no >1.1 cm.

Graphs of median and both extreme (3rd and 97th) percentiles of AFI and SDP for each racial/ethnic group by gestational week are shown in Figures 4 and 5, respectively. For both AFI and SDP, the racial/ethnic associations on the median and extreme dispersion values were most pronounced after 35 weeks of gestation, at which time maximum intergroup differences at the 3rd and especially the 97th percentiles were almost 5 cm by 40 weeks of gestation. Overall, the 3rd percentile values demonstrated less variation in absolute AFI and SDP values compared with the 97th percentiles; NHW patients had the highest 97th percentile AFI values after 27 weeks of gestation but only after 37 weeks of gestation did their 97th percentile SDP values exceed the other groups. Conversely, NHB patients had larger 97th percentile AFI and SDP values from 16−25 weeks of gestation.

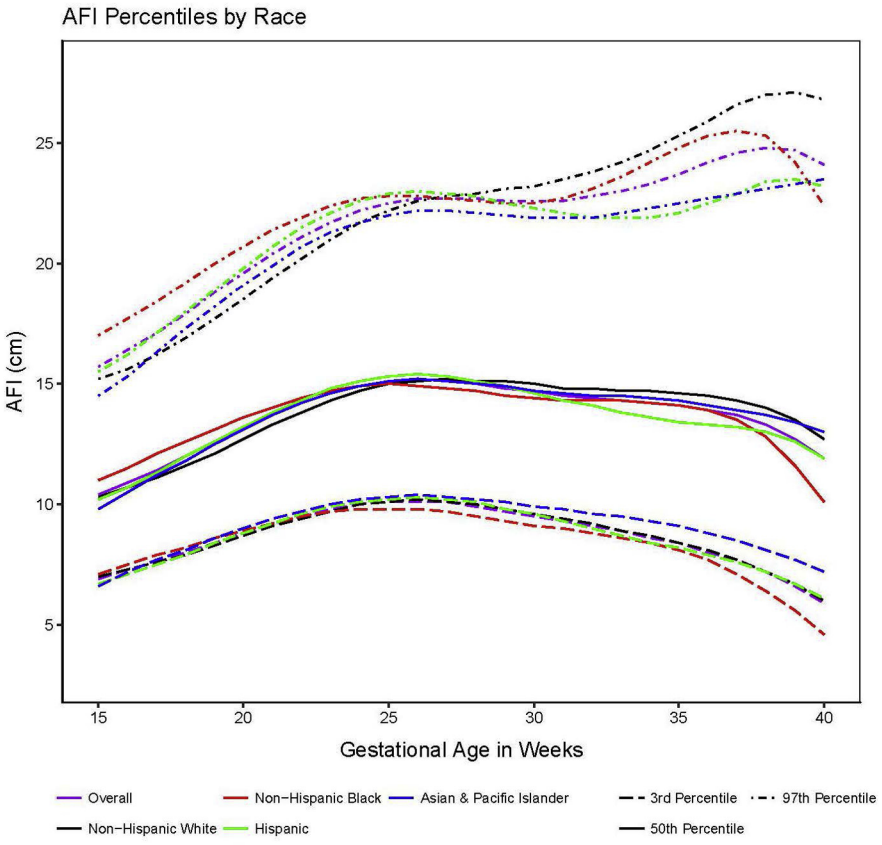
Adding the maternal characteristics (described earlier,) to the AFI and SDP models, which informed Figures 1−5 and Tables 1−2, had no appreciable effect on the racial/ethnic differences, because the global probability values remained significant and the week-specific differences were essentially unchanged (data not shown). Similarly, additional adjustment for EFW had no discernable effect on the observed racial/ethnic differences (data not shown), which indicated that these AFV differences were not explained by previously identified racial/ethnic differences in fetal growth over gestation.[21]

Comment

Principal findings

We present AFI and SDP median, percentiles, and graphic nomograms based on controlled data that were observed in a large contemporary multiracial/ethnic cohort of US women with low-risk singleton gestations. Study participants underwent serial sonographic measurements of AFI and SDP from 15−40 weeks of gestation with the use of up-to-date, high resolution ultrasound equipment. Women who were included in the analysis were selected initially to have characteristics that would be anticipated to support normal fetal growth and

FIGURE 4
Unadjusted median amniotic fluid index values and extreme (3rd and 97th) percentiles by weeks of gestation and overall and by race/ethnicity



Median plus 3rd and 97th percentile AFI curves for both the overall study population and also by the four self-reported racial/ethnic groups.

AFI, amniotic fluid index.

Owen et al. US amniotic fluid volume chart. Am J Obstet Gynecol 2019.

reasonable amniotic fluid production. The population was further refined by the exclusion of pregnancy complications. We observed statistically significant differences in both AFI and SDP across the 4 racial/ethnic groups, even after adjustment for selected maternal characteristics and the sonographic EFW. The 3rd percentile for AFI was >5.0 cm; the 3rd percentile for SDP was >2.0 cm at every gestational week. Conversely, although polyhydramnios is often defined as ≥24 cm or SDP >8 cm, in our cohort the 97th percentile for AFI was <24 cm through 35 weeks of gestation; for SDP, it was less than <8.0 cm through 33 weeks of gestation. Perhaps the most pervasive observation is that the 97th percentile in normal pregnancies varies markedly across gestation: 16 cm at 15 weeks of gestation vs 24 cm after 35 weeks of gestation.

There was observed racial/ethnic variance in the 3rd percentile values that was notable after 35 weeks of gestation, although the absolute differences were smaller than those seen at the 97th percentile. Hispanic and NHW women had values closest to the overall mean, although NHB women had approximately a 1 cm smaller value and NHB women had a 1 cm greater value; this represented the largest race/ethnic differences, which was maximal at 40 weeks of gestation.

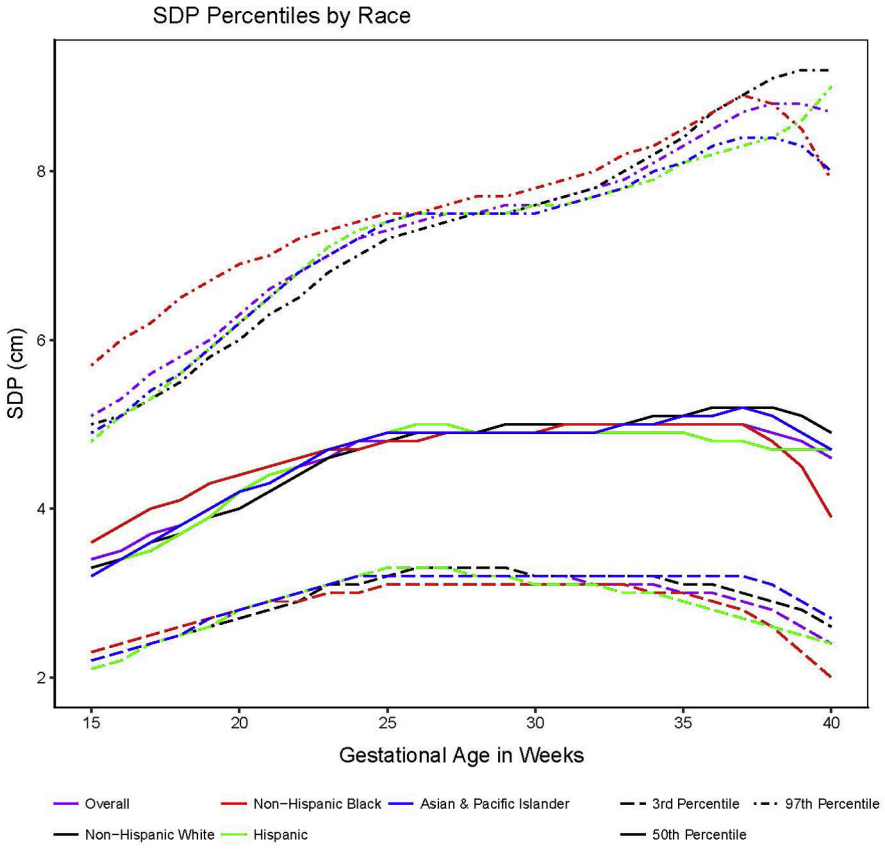
The best interpretation of the small observed differences in weekly percent changes between the AFI and SDP (Figure 3) is unclear. The 1-week delay in the initial SDP "zero" change compared with the AFI is likely of no biologic relevance and easily could represent inherent differences in AFV estimation. SDP is akin to a 1-dimensional estimate, whereas AFI may be more analogous to a 2-dimensional measurement. Thus, one might not expect perfect concordance between the 2 estimates. As a single dimensional estimate, SDP may also be influenced more by the enlarging fetal size, which would affect its estimate to a larger degree than a 4-quadrant estimate; this might explain its second (although modest increase in its peak value) from 33−37 weeks of gestation.

Meaning of the findings/clinical implications

We believe that our data should not be used to establish absolute clinical thresholds that define pathologically diminished or increased AFVs because they were derived from a normal referent population. Our findings of marked differences in the extremes of AFV across gestation may belie the use of a single AFV estimate to define oligohydramnios or polyhydramnios; although all AFI values at <35 weeks of gestation were below the commonly used cutoff of 24 cm, there were marked differences in the 97th percentiles across gestation. Similarly, the 3rd percentile values varied across gestation but with a much smaller range in absolute measurement differences.

An important question is whether our observed racial/ethnic differences in AFV, which are most evident at the percentile extremes near or at term, are clinically important. Considering the upper 97th percentile, at term, NHW women exceeded the other group values by several centimeters, although Hispanic and Asian women had the lowest measurements. These racial/ethnic differences, although not as pronounced, were also evident in the SDP value. The cause for the racial/ethnic differences in AFV is unclear, but, surprisingly, was not explained by observed racial/ethnic differences in fetal growth as estimated with the use of sonographic fetal weight. Thus, use of race/ethnic−specific values,

FIGURE 5
Unadjusted median single deepest pocket values and extreme (3rd and 97th) percentiles by weeks of gestation and overall and by race/ethnicity



Median plus 3rd and 97th percentile SDP curves for both the overall study population and also by the four self-reported racial/ethnic groups.

SDP, single deepest pocket.

Owen et al. US amniotic fluid volume chart. Am J Obstet Gynecol 2019.

although feasible, might not improve the value of surveillance and might represent an unnecessary burden to implement in clinical practice.

Strengths and weaknesses

Major strengths of the study include the ability to report measured AFI and SDP medians and other percentiles in a low-risk cohort comprised of 4 racial/ethnic groups that are representative of the current US population. Moreover, women subsequently were excluded if clinically significant pregnancy complications that were known to affect growth were discovered based on a priori criteria applied before the study results were released. Only experienced, credentialed sonographers made these measurements; AFV was a specific parameter required for credentialing. All sonograms were performed for research purposes, and the findings were not used for clinical management; however, in cases of severe oligohydramnios, this was reported. This may have led to a repeat measurement and other testing or interventions by the managing providers. Regardless, the measured AFV values from that scan would have been included in our analysis.

As with any measurement protocol, interobserver variation can affect the findings; however, this concept has been investigated and considered to be small[10,31] and consistent across studies.[32] Although interrater and intrarater reliability for AFV was not formally tested in the Fetal Growth Study accreditation process,[25] it was deemed excellent for the fetal biometrics. Thus, we have no reason to believe that this would have been different for AFV measurement. Although interobserver variability is a well-recognized limitation to essentially all biologic research where >1 observer measures a biometric parameter, the use of multiple sonographers would increase the external validity of our study compared with a single observer. Nevertheless, the variability in SDP estimation may be greater as compared with AFI,[33] although the use of sonographic estimates to diagnose oligohydramnios accurately remains a concern.[1]

Measurements were performed at perinatal centers that are well-known for clinical investigations; the ultrasound equipment was also standardized across the 12 clinical centers. The AFV measurement procedures were well-defined in the original study protocol, and these techniques have been well-standardized and in common clinical use for nearly 3 decades. Participants were assigned randomly to 1 of 4 different sonography schedules to ensure that measurements across the entire gestational range were performed and available for analysis. We used statistical models that optimized the utility of these repeated measures and further considered possible covariate effects beyond race/ethnicity.

Conclusion with future research implications

Although various cut-points to define abnormal AVF (ie, oligo- or polyhydramnios) have been published, the best cut-points to identify pregnancies with increased risk of neonatal morbidity, especially in cases of isolated oligohydramnios, remain uncertain.[34] Therefore, investigators should first establish reference charts in a low-risk, diverse population of patients who are selected to have characteristics that are associated with normal fetal growth and fetal urine production. The observed racial/ethnic differences could not be explained by selected maternal characteristics or EFW. We believe that these differences should not be considered clinically relevant until

further investigation demonstrates that inclusion of these differences as part of clinical management leads to measurable improvements in pregnancy outcomes.

In summary, compared with previous studies of AFV estimates that have used the AFI and SDP across gestation, we believe that the strengths of our study design, execution, and analysis overcome essentially all of the limitations present in previous reports of sonographically estimated AFV across gestation and could represent a legitimate US standard for sonographic AFV. Importantly, these values should not necessarily dictate clinical action points, but rather we suggest that they inform future research into the clinical implications and management of suspected amniotic fluid abnormalities. For example, the finding of an AFV estimate at the extreme might reasonably indicate the need for closer fetal surveillance that might include a subsequent (specialized) evaluation or the institution of more formal fetal surveillance (eg, biophysical profile). Given the observed variation in the dispersion extremes across gestation, the use of single value cutoffs to define out-of-range measurement estimates may not be appropriate, although this possibility will require further investigation. ■

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