Estimated Placental Volume and Gestational Age

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Abstract

Objective The objective of this study was to validate estimated placental volume (EPV) across a range of gestational ages (GAs).

Study Design Three hundred sixty-six patients from 2009 to 2011 received ultrasound scans between 11 + 0 and 38 + 6 weeks GA to assess EPV. An EPV versus GA best fit curve was generated and compared with published normative curves of EPV versus GA in a different population. A subanalysis was performed to explore the relationship between EPV and birth weight (BW).

Results Analysis of EPV versus GA revealed a parabolic curve with the following best fit equation: $EPV = (0.372\,GA - 0.00364\,GA^2)^3$. EPV was weakly correlated with BW, and patients with an EPV in the bottom 50th percentile had 2.42 times the odds of having a newborn with a BW in the bottom 50th percentile (95% confidence interval: 1.27–4.68). Microscopic evaluation of two placentas corresponding to the smallest EPV outliers revealed significant placental pathology.

Conclusion Placental volume increases throughout gestation and follows a predictable parabolic curve, in agreement with the existing literature. Further validation is required, but EPV may have the potential for clinical utility as a screening tool in a variety of settings.

Keywords
- placenta
- volume
- ultrasound
- birth weight

It is well established that the placenta plays several vital roles during pregnancy and is essential for nutrient and oxygen transfer between mother and fetus.[1] Placentas that are small for gestational age (GA) are associated with intrauterine growth restriction (IUGR), intrauterine fetal demise (IUFD), and other complications.[2–7] The relationship between small placental size and fetal complications was explored by Wolf et al in 1989, who concluded that placental growth restriction preceded fetal growth restriction and adverse events.[8] This phenomenon is also observed in the kidney in the setting of renal failure: adequate renal function can be maintained as glomerular units are damaged, until a critical number of glomeruli are injured.[9] Similarly, when a small placenta is unable to meet the metabolic needs of the growing fetus, IUFD can occur.

Despite the association between small placental size and adverse fetal outcomes, prenatal ultrasonographic evaluation of the placenta is not part of current prenatal care guidelines.[2,10] Several technical challenges could explain why measuring placental volume is not common practice: historically, methods for measuring placental volume relied on magnetic resonance imaging (MRI) or three-dimensional ultrasound

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and were time-consuming, expensive, and required extensive training.[4,11–13] However, in 2010, Azpurua et al described a technique that utilizes two-dimensional (2D) ultrasound and mathematical modeling to estimate placental volume.[10] Unlike previous techniques, the estimated placental volume (EPV) technique could be performed quickly at the bedside by a health care provider with minimal training. This approach for estimating placental volume correlates well with actual placental weights. In 2014, Arleo et al validated this method and developed normative EPV growth curves based on data from 423 patients at the Weill Cornell Medical Center.[2] In a small subset of four patients, it was demonstrated that EPV might be a useful tool for detecting abnormally small placentas.

In our study, we aimed to validate EPV versus GA in a large cohort, and compare this to normative curves generated from the Cornell data. Of note, we did not aim to show whether EPV can be used to predict birth weight (BW). Instead, our goal was to contribute to the growing literature that shows a relationship between small EPV and low BW, in an effort to promote adoption of a simple screening tool with potential clinical benefit.

Materials and Methods

This prospective observational study was approved by the Yale University School of Medicine Human Investigation Committee (protocol number 0905005157). Informed written consent was obtained for each patient. We used a method for calculating EPV that had been previously developed and validated.[2,10] The ultrasound probe was placed on the abdomen such that the entire placenta was in view. Using the measurement tool on the ultrasound machine, a line was drawn that spaned the width of the placenta. The placental height was represented by a perpendicular line drawn from the width line, extending to the apex of the placenta at the maternal surface. The placental thickness was the portion of the height line that extended from the apex at the maternal surface to the fetal surface of the placenta. Four hundred nineteen EPVs were performed on 366 patients (by trained ultrasonographers or physicians) to measure placental width, height, and thickness dimensions. This $n = 366$ represented a subset of patients who presented to the Yale New Haven Hospital (YNHH) for obstetrical care during the study period, from 2009 to 2011. The participants consisted of all comers who presented to our prenatal care center, and were not limited to low-risk or high-risk pregnancies. Of the 366 total patients, 174 patients delivered at the YNHH. For each participant, an ultrasound image of the placenta with overlaid measurements was printed and saved for future quality control review. The patients' estimated GA at the time of the scan was recorded. For this analysis, we only evaluated the first EPV collected from each patient, resulting in a set of 366 EPV data points. The GA at the time of each placental assessment, the width, height, and thickness data, as well as the calculated EPVs for all participants is shown in ►**Table 1**. For participants who delivered their infant at the YNHH, the infant's BW was recorded at the time of

Table 1 EPV data from all 366 participants in the study

GA	Width	Height	Thickness	EPV
11	8.9	1.64	2.28	74
11.1	4.58	2.46	0.83	20
11.4	5.33	2.91	1.57	40
11.4	7.49	1.57	1.14	40
11.6	6.6	2.63	2.09	58
11.7	6.73	3.14	1.89	69
11.7	7.16	3.13	1.98	78
11.9	8.65	2.71	2.37	103
11.9	5.46	3.85	1.65	55
11.9	6.4	3.08	1.37	54
11.9	7.17	1.83	1.35	44
12	7.73	3.19	2.49	97
12	6.93	3.41	1.84	77
12	7.89	3.85	1.71	103
12	6.08	2	1.08	31
12	7.12	2.67	1.4	58
12	4.64	3.59	2.13	40
12	7.59	1.19	1.19	36
12.1	4.98	4.07	2.14	52
12.1	7.02	1.94	1.78	49
12.1	5.59	1.95	2.56	32
12.1	6.47	1.94	1.66	41
12.1	7.77	2.01	1.97	63
12.1	4.9	3.11	2.05	39
12.1	7.34	2.17	1.78	58
12.1	9.1	1.99	1.76	83
12.1	5.28	1.69	0.76	18
12.1	6.54	2.21	1	36
12.1	8.77	2.15	2.15	87
12.1	8.21	2.09	1.59	67
12.3	6.53	3.43	1.51	64
12.3	5.69	1.24	1.24	21
12.3	4.49	2.87	2.02	30
12.3	5.39	1.95	1.23	26
12.3	4.05	4.69	1.91	40
12.3	6.73	2.85	2.28	66
12.4	5.82	2.98	4.77	66
12.4	8.34	3.16	2.2	107
12.4	4.02	3.45	2.08	29
12.4	5.78	3.15	2.05	53
12.4	7.73	4.13	1.55	100
12.4	5.28	3.01	1.68	41
12.4	5.63	3.42	1.77	53
12.4	8.57	1.83	1.31	61

Table 1 (*Continued*)

GA	Width	Height	Thickness	EPV
12.4	6.35	2.68	1.96	54
12.4	8.39	2.44	1.36	72
12.4	6.12	3.34	3.34	66
12.6	7.17	2.54	1.97	65
12.6	7.53	2.58	2.71	77
12.6	6	3.28	2.77	62
12.6	6.03	3.37	1.79	59
12.6	6.22	1.03	1.29	23
12.6	6.85	2.11	2.02	51
12.6	9.26	3.62	3.04	159
12.6	7.06	2.59	1.5	58
12.6	7.11	1.75	0.85	32
12.6	7.92	1.92	1.83	62
12.6	7.67	3.63	2.51	108
12.6	5.78	3.74	1.08	47
12.6	5	4.78	2.17	62
12.6	6.25	5.72	1.91	105
12.6	5.98	3.69	1.65	61
12.7	7.57	3.77	2.46	108
12.7	4.52	4.2	1.54	42
12.7	7.79	2.45	1.6	68
12.7	6.88	2.34	1.36	49
12.7	8	1.59	1.36	50
12.7	5.4	5.58	3.08	84
12.7	6.87	2.68	1.59	58
12.9	6.42	4.56	1.87	88
12.9	5.24	3.26	1.49	42
12.9	7.4	4.44	1.82	108
12.9	8.24	3.52	2.48	119
12.9	7.82	1.98	1.6	59
13	9.83	2.87	1.76	122
13	6.85	4.16	1.18	71
13	6.72	2.55	2.24	59
13	7.03	1.85	1.5	45
13	8.29	2.42	2.04	84
13.1	6.71	2.17	1.7	48
13.1	5.91	5.75	3.6	103
13.1	7.05	3.9	3.04	101
13.1	8.25	3.29	1.59	94
13.3	6.95	3.84	2.43	94
13.3	10.2	2.59	1.98	129
13.4	7.6	1.92	1.64	55
13.6	8.49	2.77	1.94	95
13.6	4.42	1.95	1.74	20

(*Continued*)

Table 1 (*Continued*)

GA	Width	Height	Thickness	EPV
13.6	8.25	2.96	2.45	102
13.6	8.73	2.94	1.69	99
13.7	8.75	3.82	2.22	138
13.7	8.66	2.97	2.58	114
13.7	5.83	4.25	3.87	75
13.9	4.33	2.66	2.09	26
13.9	8.27	1.91	1.88	68
14	8.94	2.45	1.93	96
14	7.13	3.39	1.89	81
14.9	9.9	2.48	1.7	110
14.9	8.49	2.12	1.18	62
15	10.5	2.72	2.63	156
15.4	8.43	4.09	2.76	146
15.4	8.76	2.21	1.56	78
16.3	8.3	3.11	1.77	96
16.4	12.8	2.93	2.37	232
16.4	12.1	2.46	2.46	189
16.4	9.03	2.34	2.34	100
16.9	9.97	3.44	2.62	169
16.9	11.5	4.44	2.4	260
17	9.91	3.31	1.29	113
17.4	9.12	3.5	1.66	120
17.4	12	3.88	2.24	244
17.7	8.47	3.49	2.45	124
17.7	8.86	2.17	1.44	76
17.7	9.13	4.53	2.72	185
17.7	6.19	6.22	2.18	118
17.9	11.9	2.75	3.75	214
17.9	10.23	2.41	1.32	99
17.9	11.79	2.76	2.21	185
18	5.8	7.88	2.61	138
18	10.7	2.58	2.41	152
18	10.5	2.6	2.3	145
18	10.9	4.58	2.6	251
18	9.74	3.85	2.24	168
18	10.4	2.75	2.51	152
18	10.83	2.46	2.46	151
18	9.57	2.24	1.9	101
18	7.32	4.22	3.3	118
18	11.5	2.86	1.6	153
18	9.43	4	2.95	179
18	10.5	3.12	3	179
18	7.9	2.6	0.65	40
18	10.7	2.41	2.4	144

(*Continued*)

Table 1 (*Continued*)

GA	Width	Height	Thickness	EPV
18	9.38	5.81	3.66	263
18	10	3.51	2.82	177
18	12.2	4.71	2.85	326
18.1	9.37	4.41	2.56	185
18.1	13.6	3.5	2.54	302
18.1	7.68	6.48	3.93	200
18.1	11.1	3.45	2.18	192
18.1	10.76	3.92	3.11	229
18.1	13.6	2.84	2.1	241
18.1	11.5	4.92	2.53	289
18.1	11.9	3.39	2.22	217
18.1	9.6	3.05	2.86	146
18.3	5.77	9.8	3.63	164
18.3	10.4	2.27	1.93	121
18.3	8.75	3.11	2.31	118
18.3	10.7	3.24	2.19	172
18.3	8.89	5.85	2.64	220
18.3	9.42	4.16	4.16	193
18.3	8.22	7.24	1.2	149
18.3	9.72	2.47	1.97	113
18.3	11.2	3.26	2.21	189
18.3	10.6	3.37	2.88	192
18.3	8.13	7.29	4	252
18.3	12.9	2.62	2.62	228
18.3	12.1	5.43	2.14	311
18.3	13.2	3.04	1.93	227
18.3	8.89	4.08	1.63	128
18.3	9.34	3	2.13	125
18.4	12.7	3.45	2.56	265
18.4	11.9	4.82	2.27	285
18.4	10.8	1.42	2.63	106
18.4	10.5	3.3	2.45	177
18.4	10	3.2	2.42	157
18.4	10.4	3.22	3.22	182
18.4	8.76	4.91	2.58	181
18.4	5.48	7.23	2.54	113
18.4	12.4	2.61	1.61	166
18.4	11.9	3.99	1.82	218
18.4	11.48	3.88	1.35	166
18.4	7.7	5.65	3.24	174
18.4	11.6	3.6	3.16	247
18.4	12.91	2.72	2.72	237
18.4	10.3	3.31	3.23	183
18.4	9.93	3.1	3.05	160

Table 1 (*Continued*)

GA	Width	Height	Thickness	EPV
18.4	10.9	3.89	2.64	221
18.6	13.4	3.66	3.32	336
18.6	10.7	3.81	3.75	228
18.6	10.67	5.23	1.86	227
18.6	11.3	2.39	2.38	160
18.6	8.13	6.16	2.22	185
18.6	9.14	3.64	4.9	160
18.6	11.04	2.01	1.62	116
18.6	9.94	4.86	2.49	221
18.6	11.5	2.14	0.88	85
18.6	7.83	2.36	1.84	71
18.6	11.6	2.21	2.21	156
18.6	10.45	2.95	2.09	151
18.6	9.1	4.53	4.42	196
18.6	13.6	3.49	3.32	334
18.6	10.5	2.89	2.47	160
18.6	11.1	2.76	1.62	141
18.7	11.7	3.37	2.03	201
18.7	12.7	2.3	2.82	208
18.7	9.66	2.6	2.6	127
18.7	10.7	2.67	2.22	151
18.7	13.4	3.58	2.14	274
18.7	11.9	2.81	2.15	188
18.7	11.9	5.4	1.62	252
18.7	11.7	4.82	3.03	316
18.9	5.82	8.36	7.65	115
18.9	10.4	3.11	2.81	173
18.9	10.2	3.98	3.08	209
18.9	8.83	4.53	3.89	185
18.9	14.1	3.81	2.74	355
18.9	13.13	2.94	2.43	247
18.9	12.2	2.58	2.13	186
18.9	9.76	2.2	1.45	91
18.9	10.8	2.25	1.73	123
18.9	10.65	3.16	2.02	162
18.9	4.82	4.97	1.54	55
18.9	11.38	4.44	2.94	277
18.9	12.6	3.23	2.74	255
19	12.1	2.25	2.83	185
19	9.15	2.24	4.93	99
19	12.6	2.83	1.89	197
19	11.11	4.03	2.29	222
19	9.99	3.02	2.73	155
19	10.18	3.09	3.09	168

Table 1 (*Continued*)

GA	Width	Height	Thickness	EPV
19	8.49	4.48	4.48	169
19	11.1	3.21	3.21	207
19.1	12.6	2.17	2.14	179
19.1	11.6	4.48	2.65	278
19.3	9.31	3.93	2.79	170
19.3	12.4	1.42	1.88	132
19.3	12.25	4.37	2.42	287
19.3	8.39	3.48	1.75	107
19.3	12.8	4.11	2.52	302
19.3	11.3	3.98	3.42	260
19.4	10.2	2.28	1.73	111
19.4	12.6	3.01	1.91	206
19.4	13.4	2.03	2.03	191
19.4	7.93	5.21	2.67	163
19.4	13	3.15	2.66	264
19.4	10.5	2.57	2.57	148
19.6	12.29	2.96	2.67	227
19.6	14	2.95	3.05	306
19.6	7.95	3.72	2.07	111
19.6	11.9	3.36	2.38	223
19.6	9.99	2.96	2.96	155
19.6	13.5	2.5	2.05	218
19.6	12.9	1.96	1.96	171
19.6	11.9	4.41	2.92	298
19.7	8.07	1.26	2.15	50
19.7	12.8	6.16	3.3	471
19.7	11.87	4.37	3.61	314
19.7	11.6	3.31	2.94	227
19.7	10.2	3.77	1.61	150
19.7	11.1	3.42	2.37	198
19.9	8.74	5.1	3.97	204
20	7.17	4.33	3.28	116
20	10.2	4.5	2.78	226
20	13.68	3.77	2.91	342
20	11.42	3.54	2.21	208
20	10.83	4.23	2.07	209
20	14.7	5.18	3.39	527
20.1	11.2	3.53	3.53	232
20.1	13.5	4.53	3.45	408
20.1	13.7	3.24	2.84	305
20.3	11.3	4.45	2.34	249
20.3	14.6	2.2	2.17	244
20.4	13.4	4.32	2.75	355
20.4	11.37	5.25	5.14	355

(*Continued*)

Table 1 (*Continued*)

GA	Width	Height	Thickness	EPV
20.4	13.2	2.97	2.22	241
20.4	13.2	4.52	2.48	340
20.4	10.4	3.58	3.58	203
20.6	11.5	2.51	2.75	178
20.6	12.7	4.18	3.24	334
20.6	9.74	7.15	1.42	212
20.6	12.9	3.07	2.85	262
20.6	12.7	2.09	2.09	177
20.6	13.9	5.24	2.73	436
20.7	11.3	2.34	2.34	156
20.9	10.6	8.35	4.36	484
20.9	12.7	3.52	1.6	207
20.9	14.9	4.17	2.9	430
21	13.9	2.77	1.76	223
21	10.2	1.98	1.72	102
21.1	10.5	3.6	2.59	193
21.1	12.5	3.29	2.68	253
21.1	13.4	3.9	3.05	343
21.3	13.1	4.11	2.14	289
21.3	8.52	4.29	2.24	146
21.4	12.8	2.81	2.08	213
21.6	13.4	3.44	3.08	314
21.6	15.1	3.73	2.88	406
21.7	12.9	4.11	3.17	337
21.9	13	3.7	2.86	304
21.9	14.6	2.94	1.75	251
22	13.1	3.07	3.91	288
22	10.9	4.95	2.25	250
22.1	11	4.36	4.53	277
22.1	11.2	1.92	1.87	125
22.1	11.8	3.7	3.46	267
22.3	12.6	3.33	2.41	248
22.3	5.46	9.25	1.72	128
22.4	14.7	4.25	3.45	455
22.4	9.46	3.75	2.74	167
22.4	9.39	5.46	2.84	233
22.4	12.5	2.74	2.64	221
22.6	13.1	4.32	2.66	336
22.6	15.2	4	3.48	465
22.6	12.93	3.26	2	233
22.9	13.2	3.4	1.9	241
23	11.9	3.05	2.6	216
23.1	9.99	9.92	4.63	517
23.1	7.3	6.17	3.93	172

(*Continued*)

Table 1 (*Continued*)

GA	Width	Height	Thickness	EPV
23.4	12	3.29	2.86	239
23.4	15.9	5.96	5.96	789
23.6	12.6	4.71	3.2	361
23.7	11.51	3.92	3.05	259
24	12.9	5.28	4.09	446
24	10.47	3.77	1.92	174
24.1	15.9	4.41	2.27	439
24.4	14.4	4.11	3.34	422
24.4	13.4	5.32	4.41	490
24.6	13.4	4.08	3.54	372
24.7	13.4	4.18	2.41	325
24.9	17.8	4.46	2.31	544
24.9	11.2	5.95	4.07	382
25	16.3	4.38	4.38	609
25.1	15.2	3.08	2.85	362
25.1	10.4	6.73	3.39	358
25.1	15	3.7	3.68	435
25.6	15.7	4.54	3.92	566
26.6	16.1	3.07	2.1	345
27	13.4	3.6	3.6	338
27.1	14.51	2.91	2.82	317
27.9	16	6.11	5.3	807
28	13.54	5.64	3.54	496
28.1	13.7	4.53	3.41	417
28.9	16.4	4.23	3.56	565
29.1	14.59	4.14	4.14	461
29.6	11.6	6.17	4.47	428
29.6	17.9	3.99	3.83	661
29.9	12.5	6.32	4.16	497
30	19.22	4.13	1.92	525
30.3	11.7	8.22	4	559
30.4	15.9	3.84	3.41	490
30.4	5.41	9.14	4.7	103
30.6	11.4	6.82	3.56	433
30.9	15.2	5.81	3.76	640
30.9	16.3	4.19	6.79	593
31.1	14.4	4.49	4.07	479
31.4	15.1	4.39	1.85	351
31.7	10.73	7.3	5.81	439
31.9	15.4	3.81	4.17	483
32.4	9.01	5.99	1.46	167
32.6	14	4.45	3.13	415
32.6	15.5	5.83	4.06	683
32.6	13	3.24	2.61	267
32.9	17.8	5.41	5.04	886
33.4	15.8	8.15	5.82	1,044
33.4	15.6	5.41	3.66	627
33.9	17.4	4.2	2.86	570
34.3	17.2	5.52	2.58	632
34.3	13.7	4.46	2.17	333
34.4	15.8	7.99	2.51	711
34.9	13.4	6.04	3.93	534
35.3	14.5	3.97	2.92	396
35.6	14.3	7.02	3.08	615
36.3	16.42	5.82	3.01	662
36.6	17.5	4.54	3.58	674
37	18.5	4.33	3.1	679
38.9	20.5	5.46	4.78	1,159

Abbreviations: EPV, estimated placental volume; GA, gestational age.
Note: Gestational age at the time of the placental measurements. Width, height, and thickness measurements from each placenta were used to calculate the EPV, as described in the section "Materials and Methods."

delivery. For the remaining patients who did not deliver at the YNHH, BW data were not available to the investigators. Since YNHH is a tertiary care center with a large catchment area, at the time of the scan, it was not known whether the patients would ultimately deliver at the YNHH or at an outside facility.

Inclusion criteria were as follows: any pregnant woman between 8 and 42 weeks' gestation, singleton gestation, and 18 years old or older. Exclusion criteria included: rupture of membranes, intramural fibroid, placenta previa, and women in active labor.

Using R version 3.3.2 (The R Foundation for Statistical Computing Platform) statistical software, an EPV versus GA best fit curve was generated. Subgroup analyses were performed to elucidate differences between the populations of participants who delivered at the YNHH and those who did not. In particular, the GA at which women presented for their first ultrasound scan was compared. To ensure that each patient contributed equally to the dataset, analyses, and best fit curves, only each patient's first scan was included. In addition, individual EPV versus GA curves were generated and compared for these two groups. For the 174 patients who we had BW data for, plots were generated comparing the standard residuals of EPV and BW. Small EPVs and small BWs (defined based on the plots of standard residuals of EPV and BW) were defined as a positive screening test and positive condition, respectively.

Placental pathology samples were formalin fixed and paraffin embedded, stained with hematoxylin and eosin, and examined with a Nikon Eclipse 80i microscope.

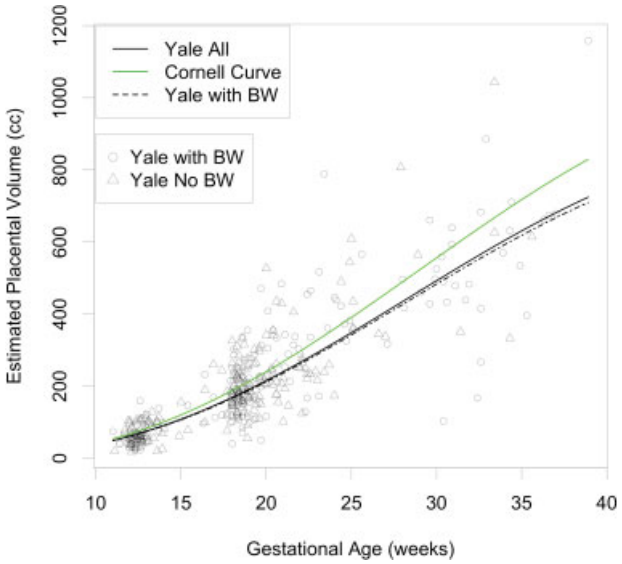

Fig. 1 Estimated placental volume (cc) versus gestational age (weeks) curves for the entire Yale dataset (solid black curve), published Cornell coefficients (solid green curve), and the Yale dataset with available BW (black dashed curve). The Yale raw data are plotted for the points that did have BWs recorded (circles) and did not (triangles). BW, birth weight.

Results

Our main objective was to explore the relationship between EPV and GA within the Yale data, and compare this to a previously published set of EPV versus GA data from Weill Cornell Medicine.[2] Both datasets demonstrated a parabolic relationship between EPV and GA (►**Fig. 1**). The previous data were best fit with the following equation: EPV = (0.384 GA − 0.00366 GA^2),[3] while our data were best fit with the following equation: EPV = (0.372 GA − 0.00364GA^2).[3] The virtual identity of the coefficients suggested that the intrinsic biology of the placentas were the same in both groups, that is, the placentas grew at similar rates in both populations as the gestations progressed.

We next explored whether there were systematic differences between the patients who delivered at the YNHH and those who did not. If a patient delivered at the YNHH, the BW was recorded. Unfortunately, we did not have BW data for patients who had EPV scans performed at the YNHH, but who delivered at outlying hospitals. However, the two datasets were very similar, both in terms of GA at EPV accrual (►**Fig. 2A**), and the best fit of EPV versus GA (►**Fig. 2B**).

We compared EPV values to BWs by plotting the standardized residuals of each parameter (►**Fig. 3**). Calculating standardized residuals normalized the data so that they could be compared in regression analyses. The majority of the data fell within ± 2.57 standard deviations for EPV and BW (red dots, corresponding to the 0.5–99.5th percentiles). Eight data points were well beyond 2.57 standard deviations (black dots). The coefficient of determination (r^2) value for all the EPV versus BW data equaled 0.063 ($p < 0.001$), black regression line, ►**Fig. 3**. When we eliminated the eight outliers, the r^2 equaled 0.054 ($p = 0.003$), red regression line, ►**Fig. 3**. Since these regression lines virtually overlapped, this suggested that the placentas corresponding to these extreme values of EPV and BW had the same intrinsic characteristics as the nonoutlier points in the dataset, and were therefore not biologically implausible.

Although dividing the data into four quadrants gives the data equal weight across the dataset, one is able to perform a 2 × 2 analysis to evaluate the potential clinical utility of the EPV as a screening tool. The result of this analysis yielded an odds ratio (OR) of 2.42 and 95% confidence interval (CI) of

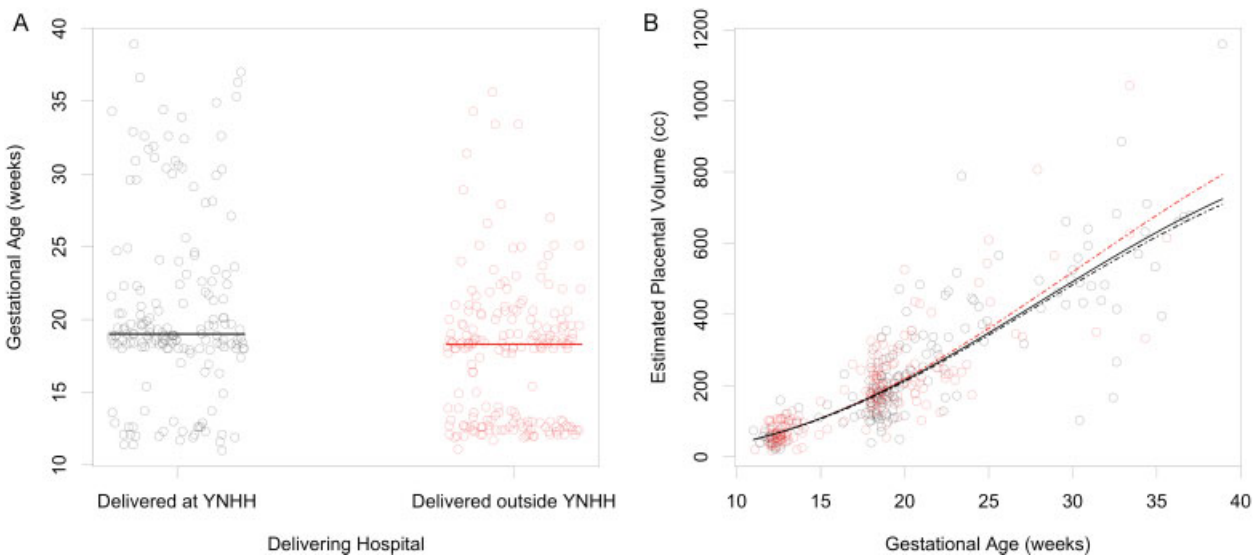

Fig. 2 Comparison of patients who delivered at the YNHH and patients who delivered outside YNHH. (**A**) Gestational age at the time of EPV performance plotted for patients who delivered at the YNHH (black) and outside YNHH (red). The solid horizontal lines represent the medians for each group. (**B**) EPV versus GA for the entire Yale dataset (black solid curve), patients who delivered at the YNHH (black circles, fitted with black dashed curve) and outside YNHH (red circles, fitted with red dashed curve). EPV, estimated placental volume; GA, gestational age; YNHH, Yale New Haven Hospital.

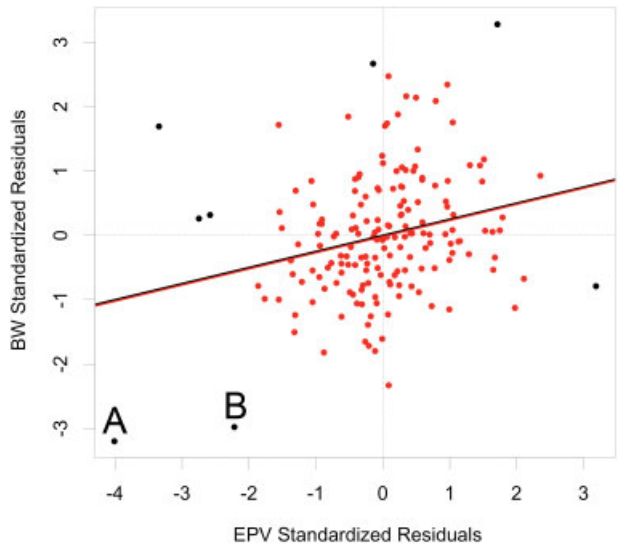

Fig. 3 Standardized residuals for EPV versus BW. The red points represent data with standardized residuals less than or equal to ± 2.57, while the black points represent residuals more than ± 2.57 (less than the 0.5th percentile or more than the 99.5th percentile). The red regression line represents the best fit to the red point data points, while the black line represents the best fit to all the data points. The outlier black data point (A) corresponds to the placenta shown in Fig. 4A, while the black data point (B) corresponds to the placenta shown in Fig. 4B. BW, birth weight; EPV, estimated placental volume.

1.27 to 4.68. This demonstrated a weak, but statistically significant, association between EPV and BW (►**Fig. 3**). Patients with an EPV in the bottom 50th percentile had 2.42 times the odds of having a newborn with a BW in the bottom 50th percentile.

Finally, we analyzed the medical records of the two most extreme outliers with the lowest EPVs and BWs to determine if they could inform us about the pathogenesis of these very small placentas. For the first case (►**Fig. 3**, lower left corner black dot), the mother was a smoker who had previously delivered an infant with IUGR. In this study, her infant had an EPV of 103 cm^3 at 30 + 3 weeks (more than 4 standard deviations below the mean). A male was delivered at 38 + 1 weeks with BW of 1,580 g (more than 3 standard deviations below the mean). Apgar scores at 1 and 5 minutes were 9 and 9, respectively. Microscopic analysis of the placenta revealed lymphocytic infiltrate of the chorionic villi, consistent with chorionic villitis (►**Fig. 4A**). For the second case (►**Fig. 3**, lower left mid-quadrant black dot), the mother had a history of Crigler–Najjar's syndrome (status–post liver transplant) and alcohol use disorder (in early remission during her pregnancy for this study). Her infant had an EPV of 269 cm^3 at 32 + 4 weeks (more than 2 standard deviations below the mean). A female was born preterm at 34 + 1 weeks with a BW of 1,010 g (almost 3 standard deviations below the mean). Apgar scores at 1 and 5 minutes were 4 and 6, respectively. Evaluation of the placenta revealed failure of conversion of the spiral arterioles (►**Fig. 4B**).

Discussion

This research study involved performing 2D ultrasound and EPV measurements on patients who presented to the YNHH for prenatal care. The EPV versus GA data were plotted and fit with a validated mathematical model previously described by authors at the Weill Cornell Medical.[2] Our EPV data were very similar to those collected at Cornell, suggesting that placental growth kinetics are an intrinsic characteristic of the placenta and not significantly influenced by patient population. Outliers should raise suspicion for intrinsic problems with the placenta (i.e., decreased maternal perfusion), or mismatch between the size of the placenta and the fetus.

Of the 366 patients where EPV studies were performed, only 174 patients eventually delivered at the YNHH, where BW was recorded. The remaining patients delivered at an outlying hospital, where BW data were not available to the investigators. We performed subgroup analyses on these two populations. We found that in fact they were very similar,

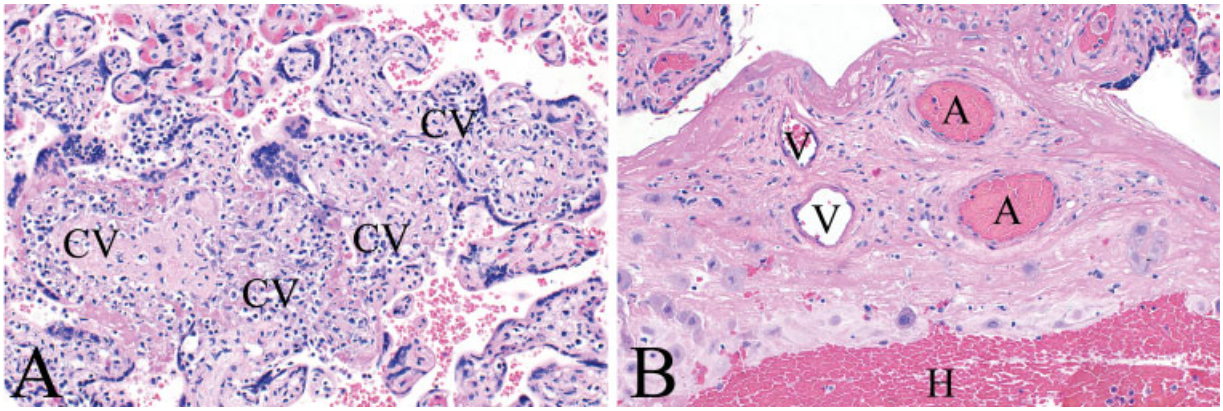

Fig. 4 Placental pathology of the two extreme EPV outlier cases highlighted in Fig. 3. (**A**) Multiple chorionic villi (CV) are agglutinated, and enmeshed in fibrin and maternal T-cells, characteristic of chronic villitis. (**B**) Junction of placenta and maternal decidua revealing normal maternal veins (V), but unconverted maternal spiral arterioles (A), a common finding in decreased maternal perfusion of the placenta. Hematoxylin and eosin staining. EPV, estimated placental volume.

with almost superimposable EPV accrual GA, and EPV versus GA growth kinetics (►**Fig. 2**). These results suggest that there was no statistically significant difference between these groups as far as EPV and GA were concerned.

When we compared EPV with BW, we found a modest relationship between these two variables. An initial crude analysis by dividing the results into four quadrants of low and high EPV compared with low and high BW resulted in an OR of 2.42 and 95% CI of 1.27 to 4.68 associating a low EPV with a low BW. The finding that EPV in the bottom 50th percentile is associated with 2.42 times the odds of BW in the bottom 50th percentile could help inform clinical decision frameworks. When we used all the data in a continuous analysis, we found a very weak correlation between EPV and BW ($r^2 = 0.063$). However, EPV was never intended to predict BW directly. Rather, since there was a weak, but statistically significant, relationship between EPV and BW, this method warrants further consideration. We propose that EPV be used to identify extreme outliers of placental volume that may be associated with IUGR, IUFD, and other adverse fetal outcomes. Analysis of the standardized residuals (►**Fig. 3**) suggested that extremely small EPVs are weakly associated with extremely low BWs. For example, EPVs below the 10th percentile might prompt placental and fetal evaluation by other imaging modalities, such as Doppler flow, MRI, or more frequent ultrasound evaluations.

Examining the two extreme EPV outlier cases illustrated the potential use of incorporating EPV into clinical practice. Both infants demonstrated IUGR. In both cases, there were several maternal variables that could contribute to adverse fetal outcomes (e.g., smoking, alcohol use, history of hepatobiliary pathology). Although these variables could potentially confound the relationship between placental size and fetal complications, it is noteworthy that EPV was extremely small in both cases. Although a small placenta is not the only cause for IUGR, examination of the placenta may be useful for routine care where specific gestational problems have yet to manifest themselves. Therefore, a larger study should be performed to evaluate the benefits of EPV in routine clinical care. In practice, there may be important underlying maternal medical conditions that the mother and obstetrician might be unaware of. In such cases, EPV could serve as a red flag to follow the mother and fetus more closely and to evaluate the placenta for underlying pathology. For example, as was seen in the outlier case B in ►**Fig. 3**, pathologic examination revealed failure of conversion of the spiral arteries, which is associated with preeclampsia and IUGR.[14] Proactive monitoring with EPV is crucial because the placenta growth restriction precedes fetal growth restriction.[8] A fetus that appears to be growing well on routine ultrasound evaluation may in fact have a small placenta, which would not be imaged or measured based on current clinical practice.

As EPV is so easy to perform, we recommend routine EPV measurements whenever the fetus is examined by ultrasound. Although the scans in this study were performed by trained ultrasonographers, EPV measurements could possibly be performed by a clinician with minimal training. Further studies would be required to support this. Of note, however, EPV measurements performed later in term may be more difficult for even expert ultrasonographers, as placentas grow significantly as GA increases. In these cases, even using a wide-angle probe to measure the placenta may present a challenge. A small EPV for GA could serve as an alert to the obstetrician to follow the mother and infant more closely.[2,10] There are differences in the clinical utility between an early EPV versus a late gestational EPV measurement. Prior to the GA of viability, there is little direct action that can be proposed in the face of a very small EPV. In those cases following the patient and fetus, possibly with increased frequency, may be the only option. However, as the patient approaches GAs with increased probability of survival, the decision for more intense fetal evaluation, and possible delivery, becomes more advantageous.

This study has several limitations. We cannot validate that EPV be used to predict BW, but we do have enough data to justify further studies. Having all of the BW data would have increased the number of patients analyzed and therefore would have increased the generalizability of the study. Second, as our patients were solicited in our routine prenatal care clinics, we had a low frequency of adverse pregnancy outcomes in the patients studied. Future studies could focus on high-risk patients where adverse outcomes are more common. Furthermore, EPV efficacy could be validated during labor and delivery triage to identify high-risk patients with very small placentas who might be inappropriately discharged due to reassuring fetal monitoring.

Unlike previous methods for determining placental volume,[10–13,15] obtaining 2D ultrasound images of the placenta and calculating EPV is fast and requires minimal cost and training. It is a robust method with demonstrated validity across different populations. As such, it has the potential for clinical utility in a variety of settings.

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