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Body mass index in fetal alcohol syndrome☆

Marilyn G. Klug, Larry Burd*, John T. Martsolf, Mary Ebertowski

North Dakota Fetal Alcohol Syndrome Center, School of Medicine and Health Sciences, University of North Dakota, Grand Forks, ND 58203, USA

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Abstract

Introduction: Prenatal alcohol exposure is an important cause of growth impairment. In this study we examined the stability of the growth measurements, including height, weight, and body mass index (BMI) percentiles, from birth to age at the time of diagnosis for subjects who were referred for evaluation to determine if they had fetal alcohol syndrome. *Methods:* We utilized subjects from the North Dakota Fetal Alcohol Syndrome Registry. Each person referred for assessment was provided a standardized assessment completed by a medical geneticist. We also examined differences in the diagnostic schema from the Institute of Medicine. The population consisted of 315 subjects with paired weight measurements, 234 subjects with paired height measurements, and 322 subjects with current BMI measurements. *Results:* Increases in weight percentiles and decreases in height percentiles were found. Children with FAS had consistently lower growth measurements. There was significant movement in and out of lower 5th and 10th percentiles by partial and no FAS children from birth to diagnosis. *Discussion:* The requirement for growth impairment needs to be broad rather than narrow, if most subjects with a diagnosis of FAS and partial FAS/ARND are to be captured.

Keywords: Fetal alcohol syndrome; Body mass index; Growth; Diagnostic criteria; Height; Weight

1. Introduction

Ethanol is a teratogen that produces a widely variable phenotype. The prototypic manifestation of the disorder is fetal alcohol syndrome (FAS) defined by the presence of growth deficiency, neuropsychological impairment and a pattern of abnormal facial features [12]. The disorder may be common. Current prevalence estimates suggest that the disorder may be as frequent as 9.1 cases per 1000 live births [11]. In contrast to other teratogenic disorders several different syndromal categorization schema are currently used by clinicians and researchers in the diagnosis of FAS and the incomplete or partial forms of the disorder. These incomplete, but not necessarily less severe, forms of the syndrome have been referred to as fetal alcohol effect (FAE), alcohol related neurodevelopmental disorder (ARND), partial FAS (PFAS) and as alcohol-related birth defects (ARBD). Most recently the terms fetal alcohol abuse syndrome (FAAS) and fetal alcohol spectrum disorder (FASD) have been suggested [1]. The current use of overlapping categorical diagnostic categories, which are meant to be mutually exclusive for FAS and the partial forms of the disorder, contrast with the widely variable expression of the physical and behavioral phenotype in FAS and the partial forms of the disorder. The diagnostic criteria for other teratogenic disorders are defined broadly. Broad criteria are necessary to include variations of the syndrome from mild to severe and to encompass the individual variation in outcomes resulting from prenatal exposure to teratogens. In contrast to FAS, ARND, partial FAS and ARBD the fetal valproate syndrome does not have several different subtypes which might be mutually exclusive. The disorder is viewed as highly variable depending on genetic susceptibility, magnitude of exposure (dose) and timing of exposure [9,10]. Thalidomide embryopathy represents another similar example of a phenotype with variable expressivity [8].

The importance of growth impairment in height and weight as an essential feature of the adverse outcome from prenatal ethanol exposure has yet to be determined. Prenatal exposure to a variety of substances can impair growth [2]. Several studies have described a relationship

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* Corresponding author. Tel.: +1-701-777-3683; fax: +1-701-777-4474.

E-mail address: laburd@medicine.nodak.edu (L. Burd).

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between prenatal alcohol exposure and growth impairment at birth and through childhood [5,7]. Day et al. [6] found that 0.2 drinks per day were associated with decreased weight at birth and that this effect was still detectable at adolescence. At 14 years of age a dose effect was found with a 3-lb decrease in weight for children born to mothers who were light drinkers (0.2 drinks per day), a 9-lb decrease in weight in children of moderate drinkers >0.2 to 0.89 drinks per day, and a 16-lb decrease in weight for the children of heavy drinking mothers (>0.89 drinks per day).

2. Methods

Each subject in the cohort was evaluated by a medical geneticist with extensive experience with FAS at one of the North Dakota Birth Defects Outreach Clinics across North Dakota. A standardized examination using the Fetal Alcohol Syndrome Diagnostic Checklist (FASDC) was completed on each subject [3]. Cases have been added to the FAS Registry continuously since 1980. All registry cases are from North Dakota. The first group was subjects with a diagnosis of FAS, the second group was diagnosed with partial FAS/ARND and the third group was subjects who were referred for an FAS evaluation but did not receive a diagnosis of either FAS or partial FAS/ARND. We compared the growth of subjects by age, gender, and magnitude of exposure by diagnostic group.

2.1. Cohort development

In this study we completed a chart review to assign a score or category for the criteria from the Institute of Medicine Report (IOM) [12]. During the chart review every 10th chart was independently reviewed. Where disagreement was present, the case was discussed and the categories were assigned by consensus. Disagreement occurred for about 7% of cases.

Paired weight and height percentiles (3rd, 5th, and 10th) from birth and diagnosis as well as BMIs at diagnosis for subjects 2 years and older were calculated using a SAS procedure provided by the Center for Disease Control and Prevention [4].

2.1.1. Statistical analysis

Paired *t* tests and repeated measures design (RMD) were used to describe the differences in the mean height and weight percentiles at birth and at diagnosis within IOM criteria, gender, and age groups. One-way ANOVAs were used to test differences in mean BMIs among IOM criteria, gender, and age groups.

Association among percentiles and IOM criteria, gender, and age groups was tested using chi-square statistics. Paired change in percentile measures from birth to diagnosis was tested using McNemar's test of change.

3. Results

3.1. Mean growth measurements

There were 315 children in the sample that had weight measurements at birth and diagnosis and 314 children with paired height measurements. We calculated BMIs for 322 children at diagnosis. Table 1 shows the mean growth measurements at birth and at diagnosis. There was a significant increase ($P<0.001$) in all paired weight percentiles between birth and diagnosis. Paired height percentiles significantly decreased for children with partial FAS ($P<0.001$), males ($P<0.001$), children 4 years and younger ($P=0.001$), and 5 to 9 years ($P=0.019$). Fig. 1 shows the average weight and height percentile

Table 1
Comparison of mean weight and height percentile ranks from birth to diagnosis

	n	Birth		Current		Within group *P*	Paired *P*
		Mean	S.D.	Mean	S.D.		
Weight							
IOM							
FAS	124	18.212	20.863	31.547	27.842	<0.001	<0.001
Partial FAS	117	28.268	25.211	45.348	32.694		<0.001
No FAS	71	39.666	27.593	56.547	28.106		<0.001
Gender							
Male	188	28.536	25.680	43.181	30.259	0.333	<0.001
Female	127	24.362	24.733	42.021	32.889		<0.001
Age							
Infant to 4	110	26.755	26.033	38.342	32.945	0.481	<0.001
5 to 9	122	26.618	25.061	45.259	28.556		<0.001
10 or older	83	27.328	25.142	44.766	32.646		<0.001
Height							
IOM							
FAS	87	33.505	31.335	30.451	27.151	<0.001	0.198
Partial FAS	91	52.088	34.064	36.291	32.006		<0.001
No FAS	54	58.677	27.833	51.196	29.670		0.066
Gender							
Male	134	51.066	31.964	37.095	29.666	0.188	<0.001
Female	100	41.000	34.221	38.037	31.770		0.196
Age							
Infant to 4	71	49.018	34.690	35.465	30.049	0.796	0.001
5 to 9	100	46.967	32.635	39.405	30.336		0.019
10 or older	63	43.903	32.890	36.760	31.629		0.069
BMI							
IOM							
FAS	120			17.072	3.353	0.014	
Partial FAS	131			18.315	3.666		
No FAS	70			17.283	3.529		
Gender							
Male	191			17.666	3.484	0.474	
Female	131			17.693	3.734		
Age							
2 to 4	85			16.037	1.386	<0.001	
5 to 9	133			16.154	1.732		
10 or older	106			20.858	4.324		

BMIs are at time of diagnosis.

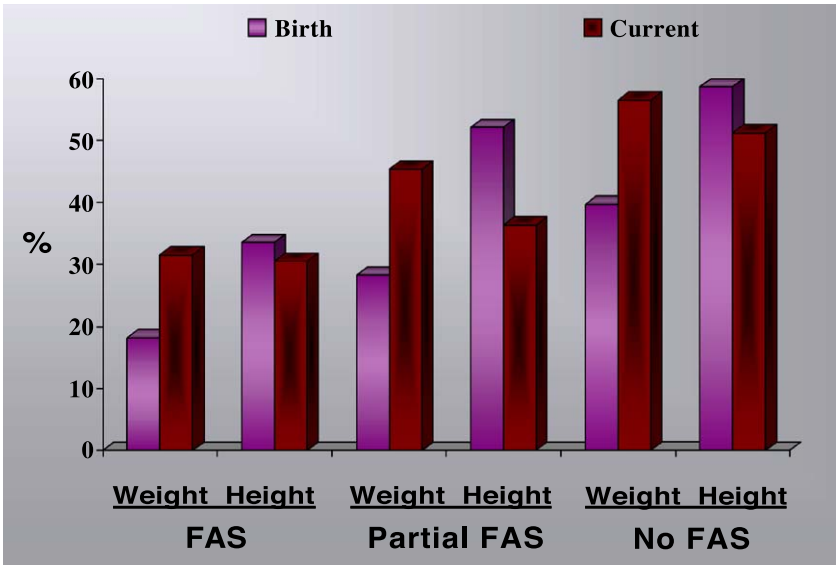

Fig. 1. Average weight and height percentile rank by IOM criteria.

ranks at birth and at the time of diagnosis by levels of IOM criteria.

Table 1 also shows the results from testing for differences in growth measurements between IOM criteria, gender, and age groups. Weight and height percentiles showed significant differences between IOM criteria ($P<0.001$), but not gender and age. Mean BMIs differed between age groups ($P<0.001$) as well as IOM criteria ($P=0.014$). Children without FAS had higher height and weight percentiles on average, though children with partial FAS had higher BMIs on average.

3.2. Growth measurements (percentile rankings)

Table 2 shows the proportion of children who were below the 3rd, 5th, and 10th percentiles for growth measurements at birth and at diagnosis by IOM criteria, gender, and age group. There were significantly more children with FAS below the 5th and 10th percentiles. Children with FAS were also more likely to be in lower birth and current weight percentiles. Males were more likely to be in lower birth weight percentiles. Children 4 years and younger were more likely to have lower current weight. A similar pattern was seen with height where children with FAS were more likely to be in the lower percentiles at birth and at diagnosis. Males also were more likely to be in the lower height percentiles at birth.

Figs. 2–4 show percentile rankings for BMI, weight, and height, respectively. Children with FAS consistently have greater proportions in the lower percentiles. These children also appear to have more stability over time, with similar proportions in the percentiles, while partial FAS and no FAS children show more increase in weight and decrease in height over time.

The number and proportion of children who moved out of a percentile ranking, or into a percentile ranking between birth and diagnosis for weight and height is shown in Table 3. There were significantly more children with partial FAS moving out of the 5th or 10th percentile for weight than moving into the percentile from birth to diagnosis. The same holds true for children without FAS at the 10th percentile. For height, the only significant change was partial FAS children moving into the fifth percentile.

Other areas where change occurred were females moving out of the three lower percentiles for birth weight and males moving out of the 10th percentile for birth weight and current weight. The only age group where significant change occurred was among the 5- to 9-year-old children were more moved out of the tenth percentile for birth weight.

Stability within each percentile rank group is shown in Fig. 5. Here, the proportion of children within each IOM criteria cohort who began at birth in a percentile and were still there at time of diagnosis is shown.

4. Discussion

Children with FAS clearly had lower growth measurements. Children without FAS had higher weight and height percentiles, though children with partial FAS had higher average BMI scores. There were no significant gender differences, and the only age differences were in BMI scores with older children having higher BMIs.

The way height and weight percentiles changed from birth to diagnosis was different. All levels of IOM criteria showed significant weight gain, increasing on average 13% to 17%. Height percentiles significantly decreased for

Table 2
Proportion of subjects in 3rd, 5th, and 10th percentiles for BMI at age of diagnosis weight, and height by IOM

	<3rd percentile		<5th percentile		<10th percentile	
	n	%	*n*	%	*n*	%
Birth weight						
IOM						
FAS	32	25.81*	41	33.06*	57	45.97*
Partial FAS	16	13.68	24	20.51	41	34.04
Not FAS	6	8.45	8	11.27	13	18.31
Gender						
Male	23	12.23*	34	18.09*	58	30.85*
Female	31	24.41	39	30.71	53	41.73
Age						
Infant to 4	25	22.73	33	30.00	40	36.36
5 to 9	15	12.30	22	18.03	45	36.89
10 or older	14	16.87	18	21.69	26	31.33
Current weight						
IOM						
FAS	27	21.77*	34	27.42*	45	36.29*
Partial FAS	13	11.11	13	11.11	24	20.51
Not FAS	2	2.82	2	2.82	3	4.23
Gender						
Male	24	12.77	28	14.89	40	21.28
Female	18	14.17	21	16.54	32	25.20
Age						
Infant to 4	23	20.91*	24	21.82	34	30.91*
5 to 9	11	9.02	15	12.30	20	16.39
10 or older	8	9.64	10	12.05	18	21.69
Birth height						
IOM						
FAS	21	24.14*	22	25.29*	30	34.48*
Partial FAS	6	6.59	7	7.69	16	17.58
Not FAS	2	3.70	2	3.70	3	5.56
Gender						
Male	8	5.97*	10	7.46*	18	13.43*
Female	21	21.00	21	21.00	31	31.00
Age						
Infant to 4	11	15.49	11	15.49	17	23.94
5 to 9	11	11.00	13	13.00	19	19.00
10 or older	7	11.11	7	11.11	13	20.63
Current height						
IOM						
FAS	16	18.39*	17	19.54	30	34.48*
Partial FAS	13	14.29	15	16.48	25	27.47
Not FAS	1	1.85	3	5.56	6	11.11
Gender						
Male	15	11.19	17	12.69	33	24.63
Female	15	15.00	18	18.00	28	28.00
Age						
Infant to 4	10	14.08	13	18.31	22	30.99
5 to 9	12	12.00	12	12.00	22	22.00
10 or older	8	12.70	10	15.87	17	26.98

* Chi-square significant at $P<0.05$.

children with partial and no FAS, particularly the children with partial FAS, which dropped an average of 16%.

Children with FAS showed little change in lower percentile ranking between birth and diagnosis for height or weight. Children with partial FAS showed the most movement, moving out of the 5th and 10th weight percentiles and into the fifth height percentile. It would appear from these data that while all three groups increase weight percentile rank from birth to diagnosis, the partial and no FAS groups decrease in percentile ranks for height.

Less than half of the children with FAS and a third or less of the children with partial FAS can be correctly identified using just growth percentiles as a diagnosis of FAS. Table 4 shows the results of a sensitivity and specificity analysis using 3rd, 5th, and 10th percentiles as cutoffs for growth measurements to determine FAS, partial FAS, or not FAS. Sensitivity ranged from 4 to 46, all very low, indicating that using these percentiles would miss many children with FAS or partial FAS (a high false negative error rate). The specificities are all high, ranging from 71 to 100, showing that these percentiles are not likely to cause someone to be diagnosed when they should not. The low sensitivities, even using the 10th percentile, are a concern, and suggest that rigid adherence to growth parameters would decrease diagnostic accuracy.

This study has several important limitations. All subjects were diagnosed by a single clinician. If a bias is present, it would likely be present in nearly all subjects. The scores from the FASDC scale were considered in the initial diagnosis, which was one of the inclusion criteria for entry into the registry. All subjects in this study were from North Dakota. This may limit the generalizability of the results. Since growth impairment is an important component of the classification of subjects in all three systems, a substantial degree of coherence between the three diagnostic schemas was expected and was found. The differences found here may underestimate the differences in the diagnostic systems, if all three were applied simultaneously.

It has been previously reported that the signs of FAS and the related disorders become less distinctive during adolescence and into adult life. This study does offer some support for this observation. It is possible that the differences in BMIs would be detected if a control group

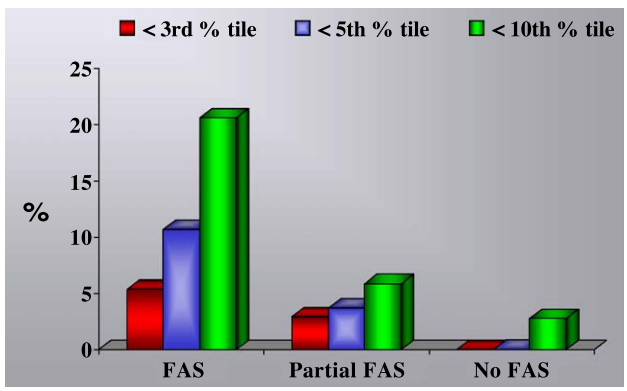

Fig. 2. BMI percentile rank by IOM criteria.

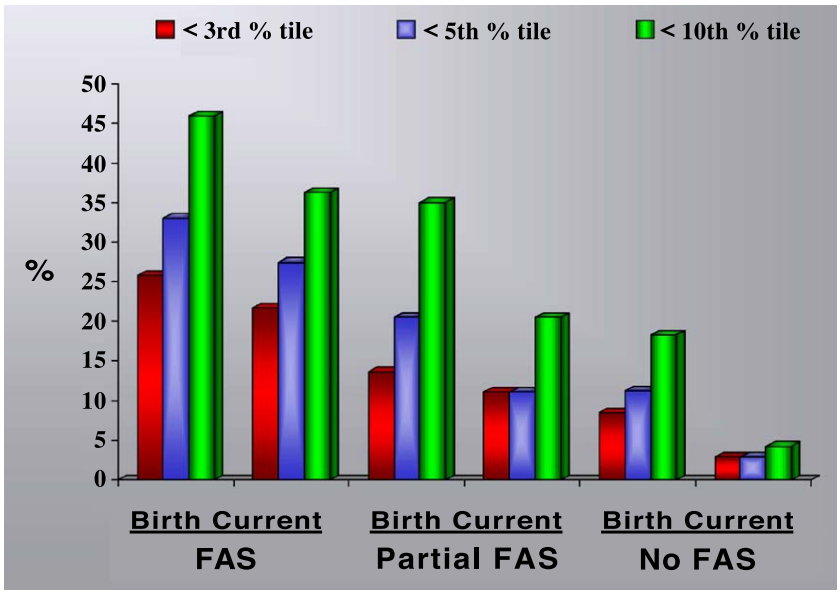

Fig. 3. Birth and current weight percentile rank by IOM criteria.

of unexposed children had been included. However, if detection of growth impairment does require inclusion of a control group to identify growth impairment for a substantial proportion of the exposed subjects, the value of growth impairment in a clinical setting is limited. It may be that growth impairment is useful primarily in more severely affected subjects. The studies by Day et al. [7] seem to offer support for both of these concepts. The finding that the growth impairment is modestly stable over time is evidence for a decrease in effect. A 6-lb difference in weight between cases and controls that is stable would actually represent a decrease in effect size as subjects grow and the proportion of their total weight represented by the case control population difference decreases. Thus, as exposed subjects become older the decrease in actual group differences for weight or height would require increasing severity for older subjects to meet a criterion for growth impairment. This would have the undesirable effect of making it very difficult for a subject to meet the diagnostic criteria for growth impairment. As a result even with stable or worsening neuropsychiatric impairment it would be difficult for clinicians

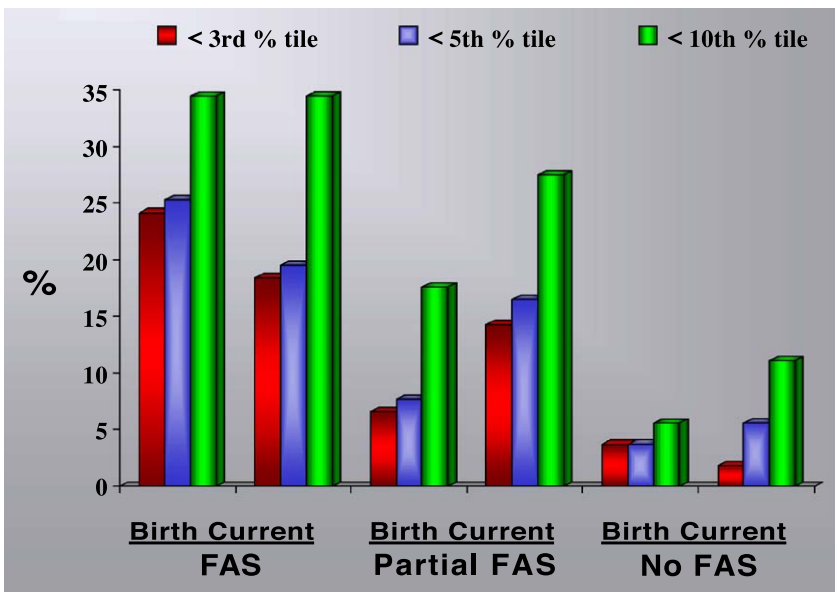

Fig. 4. Birth and current height percentile rank by IOM criteria.

Table 3
Proportion of subjects who changed weight and height percentile rankings between birth and current measurements by IOM criteria, gender, and age group

	3rd percentile				5th Percentile				10th Percentile			
	Moved out		Moved in		Moved out		Moved in		Moved out		Moved in	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Weight												
IOM												
FAS	18	14.52	13	10.48	24	19.35	17	13.71	30	24.19	18	14.52
Partial FAS	12	10.26	9	7.69	18	15.38	7	5.98*	28	23.93	11	9.40*
No FAS	6	8.45	2	2.82	8	11.27	2	2.82	12	16.90	2	2.82*
Gender												
Male	16	8.51	17	9.04	23	12.23	17	9.04	37	19.68	19	10.11*
Female	20	15.75	7	5.51*	27	21.26	9	7.09*	33	25.98	12	9.45*
Age												
Infant to 4	13	11.82	11	10.00	18	16.36	9	8.18	18	16.36	12	10.91
5 to 9	11	9.02	7	5.74	17	13.93	10	8.20	35	28.69	10	8.20*
10 or older	12	14.46	6	7.23	15	18.07	7	8.43	17	20.48	9	10.84
Height												
IOM												
FAS	15	17.24	10	11.49	14	16.09	9	10.34	12	13.79	12	13.79
Partial FAS	3	3.30	10	10.99	4	4.40	12	13.19*	7	7.69	16	17.58
No FAS	2	3.70	1	1.85	2	3.70	3	5.56	1	1.85	4	7.41
Gender												
Male	6	4.48	13	9.70	7	5.22	14	10.45	9	6.72	24	17.91*
Female	14	14.00	8	8.00	13	13.00	10	10.00	11	11.00	8	8.00
Age												
Infant to 4	6	8.45	5	7.04	5	7.04	7	9.86	5	7.04	10	14.08
5 to 9	8	8.00	9	9.00	9	9.00	8	8.00	9	9.00	12	12.00
10 or older	6	9.52	7	11.11	6	9.52	9	14.29	6	9.52	10	15.87

* Mcnemar's test for change significant $P < 0.05$.

to diagnose subjects who at an earlier point in their life may have had more growth impairment but stable neuropsychiatric impairment. Inclusion of growth impairment as a diagnostic requirement may be even more problematic in a disorder like FAS where many more mild than severe cases are present and where the signs of the disorder that produce most of the impairment (neuropsychiatric disorders) are often undervalued if the features of growth impairment (height and weight) are not present. It does seem likely that growth parameters utilized in the diag-

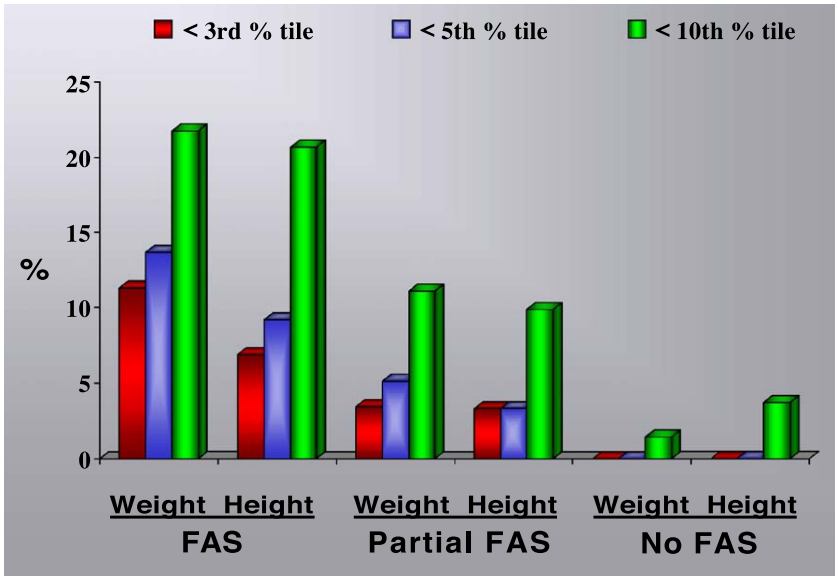

Fig. 5. Stable weight and height percentile rank by IOM criteria.

Table 4
Sensitivity and specificity of percentile cutoffs for FAS

	Sensitivity	Specificity	FPER	FNER	PPV	NPV	LR+	LR−
FAS to others								
Birth weight								
3rd percentile	25.8	88.3	11.7	74.2	59.3	64.3	2.20	0.84
5th percentile	33.1	83.0	17.0	66.9	56.2	65.3	1.94	0.81
10th percentile	46.0	71.3	28.7	54.0	51.4	66.7	1.60	0.76
Current weight								
3rd percentile	21.8	92.0	8.0	78.2	64.3	64.1	2.73	0.85
5th percentile	27.4	92.0	8.0	72.6	69.4	65.8	3.44	0.79
10th percentile	36.3	85.6	14.4	63.7	62.5	67.1	2.53	0.74
Birth height								
3rd percentile	24.1	94.5	5.5	75.9	72.4	67.5	4.37	0.80
5th percentile	25.3	93.8	6.2	74.7	71.0	67.7	4.07	0.80
10th percentile	34.5	86.9	13.1	65.5	61.2	68.9	2.63	0.75
Current height								
3rd percentile	18.4	90.3	9.7	81.6	53.3	64.9	1.90	0.90
5th percentile	19.5	87.6	12.4	80.5	48.6	64.5	1.57	0.92
10th percentile	34.5	78.6	21.4	65.5	49.2	66.7	1.61	0.83
BMI								
3rd percentile	5.3	98.0	2.0	94.7	60.0	64.0	2.58	0.97
5th percentile	8.8	98.0	2.0	91.2	71.4	64.9	4.30	0.93
10th percentile	16.7	95.4	4.6	83.3	67.9	66.3	3.63	0.87
FAS and partial FAS to others								
Birth weight								
3rd percentile	19.9	91.5	8.5	80.1	88.9	25.2	2.36	0.88
5th percentile	27.0	88.7	11.3	73.0	89.0	26.4	2.39	0.82
10th percentile	40.7	81.7	18.3	59.3	88.3	28.9	2.22	0.73
Current weight								
3rd percentile	16.6	97.2	2.8	83.4	95.2	25.6	5.89	0.86
5th percentile	19.5	97.2	2.8	80.5	95.9	26.2	6.92	0.83
10th percentile	28.6	95.8	4.2	71.3	95.8	28.3	6.78	0.74
Birth height								
3rd percentile	15.2	96.3	3.7	84.8	93.1	25.6	4.10	0.88
5th percentile	16.3	96.3	3.7	83.7	93.5	25.9	4.40	0.87
10th percentile	25.8	94.4	5.6	74.2	93.9	27.9	4.65	0.78
Current height								
3rd percentile	16.3	98.1	1.9	83.7	96.7	26.2	8.80	0.85
5th percentile	18.0	94.4	5.6	82.0	91.4	25.9	3.24	0.87
10th percentile	30.9	88.9	11.1	69.1	90.2	28.1	2.78	0.78
BMI								
3rd percentile	4.1	100	0	95.9	100	23.0	–	0.96
5th percentile	5.8	100	0	94.2	100	23.3	–	0.94
10th percentile	10.8	97.1	2.9	89.2	92.9	23.8	3.72	0.92

nosis of FAS need to be broad rather than narrow and that the criteria need to broaden as subjects age. It should also be considered that use of a criterion that is difficult, if not impossible, to detect in a clinical setting and which becomes less evident as subjects age may represent a detriment to accurate diagnosis of a disorder.

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