Analysis of Facial Shape in Children Gestationally Exposed to Marijuana, Alcohol, and/or Cocaine

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ABSTRACT. The association between fetal marijuana and/or alcohol exposure and facial features resembling fetal alcohol syndrome was investigated in a sample of 80 children. Standardized lateral and frontal facial photographs were taken of 40 children, 5 to 7 years of age, whose mothers reported frequent use of marijuana during the first trimester of pregnancy and 40 children whose mothers reported no use of marijuana during pregnancy. The marijuana-exposed and unexposed children were group-matched on alcohol exposure prior to and during pregnancy, sex, race, and age at the time of assessment. The photographs were assessed clinically by a study staff dysmorphologist and morphometrically by computerized landmark analysis. Fetal alcohol syndrome-like facial features were not associated with prenatal marijuana exposure in this study sample. No consistent patterns of facial features were identified among the marijuana-exposed group. Maternal consumption of two or more ounces of alcohol per day, on average, in early gestation was found to be associated with fetal alcohol syndrome-like facial features identified both clinically and morphometrically. Cocaine use reported by 13 of the 80 women was independently associated with mild facial dysmorphic features of hypertelorism and midfacial flattening. The results demonstrate the usefulness of this diagnostic technique for quantifying anomalies apparently unique to fetal alcohol syndrome and for targeting clusters of anomalies in new conditions for future evaluation. *Pediatrics* 1992;89:67–77; *marijuana, cocaine, alcohol, facial morphology, fetal alcohol syndrome, fetal exposure.*

Delta-9-tetrahydrocannabinol, the principal psychoactive component of marijuana, is known to cross the placental barrier in humans[1] and therefore has the potential for adversely affecting fetal development. Marijuana is estimated to be used by 1 in every 10 pregnant women. A few studies have presented evidence suggesting an association between fetal marijuana exposure and facial anomalies that resemble those seen in fetal alcohol syndrome (FAS).[2–4] Facial anomalies associated with FAS include a hypoplastic philtrum, thin upper lip, a short nose relative to the midface length, short palpebral fissues, and a flattened maxillary region. The results of these studies suggested that features compatible with FAS may not be specific to alcohol. Small sample sizes, questionable reliability of exposure, other drug use, and/or limited diagnostic sensitivity have precluded drawing firm conclusions from these studies.

In this study, the association between first-trimester fetal marijuana exposure and FAS-like facial anomalies was investigated in photographs of 40 children exposed frequently to marijuana during the first trimester of gestation. The exposure data had been collected prospectively and the association between marijuana and alcohol exposure was effectively eliminated by group-matching. Diagnosis of facial form was assessed clinically by a dysmorphologist and morphometrically by landmark analysis. The sensitivity of the morphometric diagnostic tool has been confirmed in studies of craniofacial malformation[5,6] and has effectively delineated the FAS face in a study sample half the size of the current study population.[4]

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METHODS

Subjects

Subjects in the present study were selected from among 1100 mother-infant pairs who participated in a Seattle-based prospective study (1982 through 1987) investigating the effect of maternal diet, drinking, smoking, and marijuana use during lactation on infant growth and development. There were three parts to the original prospective study. First, validity of self-reported alcohol, tobacco, and other drug use and the reliability of the maternal interview process was confirmed.[7,8] Next, descriptive studies were conducted to contrast the dietary habits and alcohol and tobacco use of lactating and nonlactating women.[9–11] And finally, two infant assessment studies were conducted to investigate the influence of alcohol and marijuana use during lactation on infant development at 1 year of age.[12,13]

The subjects' mothers in the original prospective studies were members of Group Health Cooperative of Puget Sound, a Health Maintenance Organization in Seattle, Washington. All prenatal patients receiving care between May 1, 1982, and July 1, 1984, were contracted by the Cooperative in their sixth month of pregnancy regarding possible study participation. Seventy-four percent (5298) of the prenatal patients responded positively and completed a mailed screening questionnaire detailing their alcohol and tobacco use both before and during pregnancy, some dietary information, and their plans to lactate. These patients constituted the screened pool.

A total of 1100 women were selected from the screened pool to participate in one or more of the previous prospective studies. At 6 weeks after delivery, a detailed personal interview was conducted in each woman's home to obtain information on diet, drinking, smoking, and other drug use during pregnancy and the first postpartum month. Additional information on maternal demographics and reproductive history was collected. Similar data were collected in interviews conducted at 3 and 12 months postpartum. Neonatal status (birth weight, birth length, head circumference, gestational age, and Apgar scores at 1 and 5 minutes) was abstracted from the infants' medical records.

Among the 1100 mothers, 61 reported using marijuana at least once per week during the first trimester of pregnancy and 933 reported no use of marijuana at any time during pregnancy. The children of these 61 mothers made up the exposed cohort in the present study. An equal number of children unexposed to marijuana were selected from the group of 933 by group-matching to the exposed cohort on the following characteristics: reported maternal alcohol consumption during the month prior to pregnancy and during pregnancy and the infant's sex, race, and birth date. Group-matching was performed by stratifying the 933 children simultaneously by sex, age (divided into 6-month groups), race (black, nonblack), and maternal alcohol consumption (AA score: absolute ounces of alcohol per day) both before and during pregnancy, grouped as follows ($AA < 0.05$; $0.05 \leq AA \leq 1.9$; and $2.0 \leq AA \leq 4.0$). Matches were randomly selected from the appropriate groups with the aid of a random number chart. Letters of invitation were sent to the 61 exposed subjects regarding possible study participation. Informed consent was obtained after a full explanation of study procedures. When an exposed subject was successfully located and enrolled in the study, a letter of invitation was sent to the mother of a group-matched unexposed subject. Of the 61 marijuana-exposed mother-child pairs who were eligible for participation in the study, we were able to locate and enroll 40.

Data Collection in the Original Prospective Study

Detailed information on maternal use of alcohol, tobacco, marijuana, cocaine, and other licit and illicit drugs during pregnancy was collected by personal interview at 1 month postpartum. Demographic characteristics and obstetric history were also collected. The interviewers were women of childbearing age, trained to obtain valid and reliable information. Information about maternal use of alcohol in the month prior to conception was collected in a mailed screening questionnaire completed during the sixth month of pregnancy. Use of marijuana and/or cocaine in the month prior to pregnancy was not recorded in this study. Validity of self-reported drug use was confirmed in an earlier pilot investigation of 108 randomly selected postpartum women. Self-reported drug use was compared to laboratory tests of drug levels present in body fluids. The proportion of questionable self-reports ranged from 0% to 3% depending on the drug.[7]

Information about maternal use of marijuana and cocaine was recorded in terms of how often the substance was used (days per week) and how many "joints" or "snorts" were taken per day when the substance was being used. This information was recorded for each trimester. Alcohol consumption was categorized into beer, wine, and liquor and was recorded in terms of frequency of use (days per week), modal quantity, and maximum quantity per drinking occasion in the month prior to conception and during each trimester. These measures were converted to average daily ounces of absolute alcohol ingested per day (AA score).[14]

Assessment of Facial Photographs

Photographic Procedure. An informed consent with a full explanation of study procedures was provided for the parent or guardian and an assent form was provided for the child. Facial form was assessed from standardized frontal and lateral facial photographs. The children were between 5 and 7 years of age at the time of the photograph. A placard with the child's study number and a 2-cm rule was included in each photograph to provide a measure of scale. The children were asked to hold a comfortable pose with their mouths closed while the photographer positioned herself to obtain frontal and lateral pictures with no detectable rotation. The photography session took approximately 20 minutes.

A set of 5 × 7- and 2 × 3-inch, black and white prints were made of each frontal and lateral view. The photographs within each set were printed to scale, within 1 mm accuracy, so that distance measures taken directly from the photographs would be comparable across all the subjects. The larger prints were used for digitization of facial landmarks and measuring distances between landmarks while the smaller prints facilitated the clinical evaluation, permitting scanning of the entire group of photographs at one time.

Clinical Assessment of the Photographs. The photographs of all 80 children were examined and scored by the study staff dysmorphologist (S.K.C.). The photographs were first evaluated for the presence of FAS-like facial features and then for any other pattern of anomaly. Specific attention was given to short palpebral fissues, absent or diminished philtrum, thin upper lip, short nose relative to the midface height, and flattening of the maxillary region. The assessments were performed without knowledge of exposure history. The measures recorded from the 5 × 7 photographs of each child include midface height (entrocanthion to upper lip), nose length (entrocanthion to subnasale), intercanthal distance, palpebral fissure length, philtrum and midface contour (scored as "not," "somewhat," or "definitely flat"), upper lip (scored as "not," "somewhat," or "definitely thin"), and ptsosis (present, absent).

Based on the above measures and the dysmorphologist's overall impression of the child's face, each child was classified into one of the following five groups: (1) no unusual features; (2) unusual features, but not the face of FAS; (3) possible FAS-like face; (4) probable FAS-like face; or (5) definite FAS-like face.

Computerized Morphometric Assessment of the Photographs Using Landmark Analysis. A set of 23 facial landmarks were located and marked on the 5 ×.7 photographs of each child (Fig 1, Table 1). These are the same landmarks that were used in the previous study by Clarren et al.[4] The relative location of the 23 landmarks was entered into a data base with the use of a computer digitizing tablet (MacTablet).

An analysis of facial shape was carried out using methods developed by Bookstein.[15-19] The analysis began with the examination of triangles defined by sets of three landmarks; the mean shapes of these triangles were compared between the exposed and unexposed groups. For example, if a short midface was the facial characteristic of interest, then the triangle resulting from the three facial landmarks 1, 4, and 12 might describe that characteristic (Fig 2). The triangle would be standardized by arbitrarily selecting one edge, for example 1-4, as the baseline and assigning it a standard length of one unit on a Cartesian (x, y) coordinate system (Fig 2). The shape of the triangle would be described by the x and y "shape coordinates" of the third landmark (number 12). The x, y shape coordinates for the triangles of each exposed and unexposed subject could then be displayed in a scatterplot and the mean shape coordinates for each group would be computed as the average (or centroid) of the scatter of shape coordinates within each group (Fig 3). In this hypothetical example, the mean location of landmark 12′ for the exposed group is closer to the baseline 1-4 than the mean location of landmark 12 for the unexposed group. Hotelling's T^2 statistic would be used to determine whether this observed difference in mean shape between the two groups of triangles is significant.

After identifying which triangle(s) had significantly different mean shapes between two groups, a description of how the triangles differed was formulated using tensor analysis. The difference in shape between two triangles can be characterized by a pair of directions at 90°: those for which measured distances show the greatest and least relative charge (expansion or contraction). This pair of directions, drawn to depict the magnitude as well as the direction of shape change, are called "tensor axes" (Fig 4). Tensor

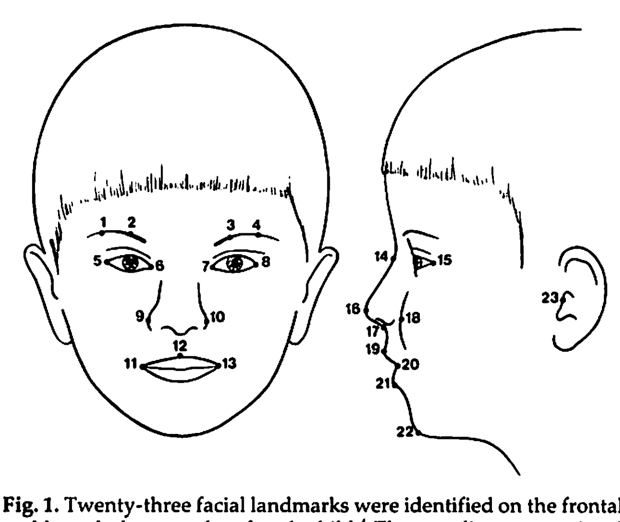

Fig. 1. Twenty-three facial landmarks were identified on the frontal and lateral photographs of each child.[4] The coordinates associated with each landmark were entered into a data base by computer digitization. The landmark definitions are presented in Table 1.

TABLE 1. Definition of the Facial Landmarks*

Landmark	Common Name	Definition
		Frontal view
1, 4		Intersection of the eyebrow curve and a vertical line through the exocanthion
2, 3		Intersection of the eyebrow curve and a vertical line through the midpoint of the palpebral fissure
5, 8	Exocanthion	Lateral intersection of upper and lower eyelids
6, 7	Entrocanthion	Medial intersection of upper and lower eyelids
9, 10		Most lateral points on alar curvature
11, 13	Cheilon	Lateral intersection of upper and lower vermilion
12		Midpoint of upper vermilion border
		Lateral view
14	Nasion	Point of maximum curvature over nasal bridge
15	Exocanthion	Lateral intersection of upper and lower eyelids
16	Pronasale	Point of maximum curvature over nasal tip
17	Subnasale	Intersection of columella and philtrum
18		Point of maximum curvature of soft tissue fold from zygoma
19		Border of upper vermilion and philtrum
20	Cheilon	Lateral intersection of upper and lower vermilion
21		Border of lower vermilion and lower lip
22	Gnathion	Point of maximum curvature of chin
23		External auditory opening

* The facial landmarks are illustrated in Fig. 1.[4]

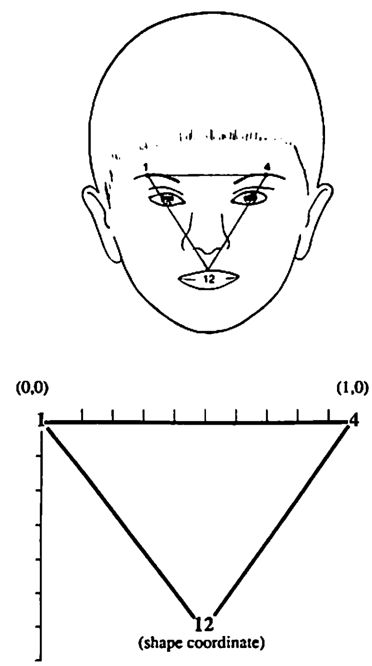

Fig. 2. The triangle formed by the three facial landmarks 1-4-12 is standardized on a cartesian (x, y) coordinate system. Landmark number 12 represents the x, y shape coordinates for this triangle.

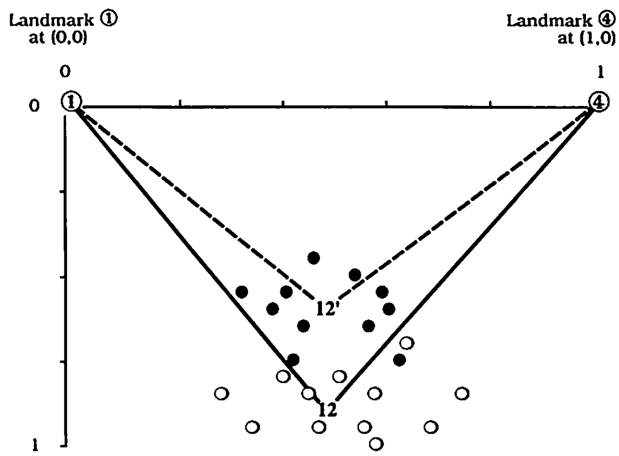

Fig. 3. The shape coordinates (landmark 12) of the exposed (●) and unexposed (O) subjects are displayed as a scatterplot in this hypothetical example. The scatterplot graphically illustrates the position of the midpoint of each child's upper vermilion border (landmark 12) relative to the position of landmarks 1 and 4 on the eyebrows. The *mean* shape coordinates for each group are represented by the average (or centroid) of the scatter of shape coordinates within each group. The locations of the mean shape coordinates for the exposed and unexposed groups are represented by 12′ and 12, respectively. The observed difference in shape between these two mean triangles would be assessed using Hotelling's T^2 statistic.

analysis of landmark data has been described in detail in several publications by Bookstein.[15,16,20] Its application to the study of FAS has also been described.[4,19,21] The use of tensor axes to describe shape change between individual triangles can be extended to describe shape change across the entire set of landmarks using the method of biorthogonal grids.[18,20,22,23] No single triangle of landmarks can be studied independently of the configuration of landmarks around it. Indeed, pictures of tensor axes for triangles can be misleading.[19] Biorthogonal grids (as demonstrated in Fig 8A) depict tensor axes which vary smoothly from place to place over the image. A grid consists of two families of curves which intersect everywhere at 90°. These intersecting curves indicate the directions of greatest (relative) expansion and contraction for a smooth mapping of one landmark configuration into another.

Statistical Analysis

In a previous study,[4] the mean facial shape coordinates associated with triangles 1-4-12, 22-14-19, and 19-23-14 were found to be significantly associated with high levels of prenatal alcohol exposure. These particular triangles were first analyzed to determine whether they differentiated the marijuana- or the alcohol-exposed groups from the unexposed groups in this study. Other triangles, with shapes not so clearly related to FAS, were next evaluated. Because of the exploratory nature of that assessment, formal tests of hypotheses were not emphasized.

The independent and interactive effects of fetal marijuana and alcohol exposure on the x and y coordinate values describing facial shape were assessed by multivariate analysis of variance.[24] Within the context of multivariate analysis of variance, Hotelling's T^2 statistic was used to test explicitly for differences in mean shape between the marijuana- and alcohol-exposed and unexposed groups. To test whether shape changes across all possible triangles, as depicted in the biorthogonal grid, could be described by a simple linear (or homogeneous) model of deformation, another variant of Hotelling's T^2 statistic was used.[19] Under this model, the tensor axes for shape change are the same for all possible triangles.

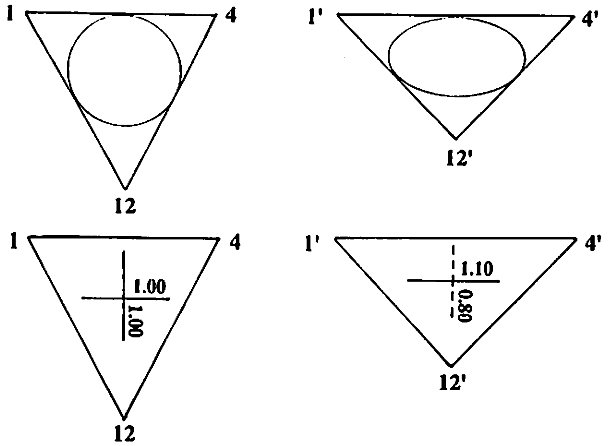

Fig. 4. The transformation of one triangle into another transforms[18] a circle inscribed in the first triangle into an ellipse in the second. The axes (or tensors) of the ellipse, rescaled and oriented homologously in triangle (1-4-12), lie along the directions in which that triangle is most stretched and most compressed by the transformation. The magnitude of the stretching and compression is reflected in the length of the axes. In this hypothetical example, the "deformed" triangle 1'-4'-12' representing the mean shape of the exposed group resulted from a 10% horizontal expansion and a 20% vertical contraction of the "normal" triangle 1-4-12 representing the mean shape of the unexposed group.

Differences in maternal characteristics and infant outcomes between the marijuana- and alcohol-exposed and unexposed groups were evaluated by χ^2 and the t test, where appropriate. Multiple regression analysis was used to evaluate associations between marijuana and alcohol exposure on birth outcome measures and distance measures recorded from the photographs.

RESULTS

Study Population

Of the 61 marijuana-exposed children who were eligible for participation in this study, we were able to locate and enroll 40. These subjects had been last contacted 5 to 7 years previously, when they participated in the original prospective study. Of the 21 mother-child pairs that were not enrolled, 9 could not be located, 2 had moved out of state, 9 were contacted but did not want to participate in the study, and 1 infant had died of sudden infant death syndrome. The mothers of the 40 children who were enrolled in the study differed from the mothers of the 21 children who did not participate in that they were heavier users of marijuana, alcohol, and tobacco and were less likely to have attended college.

From among the 933 eligible nonexposed subjects, the mothers of 70 children were contacted in order to locate and enroll 40 group-matched subjects. Of the 30 subjects who were not enrolled, 24 could not be located, 1 had moved out of state, and 5 expressed no interest in participating in the study. The 40 children with no reported exposure to marijuana were effectively group-matched to the marijuana-exposed group on preconceptional and prenatal alcohol exposure, sex, race, and birth date. Women who reported use of marijuana were, however, more likely to be younger and to be in a lower income bracket and were less likely to be married or to have attended college (Table 2).

Among the 40 marijuana users, 15 reported using marijuana one to two times per week, 11 reported using it three to four times per week, and 14 reported using it every day (Table 3). Fifteen of the women reported smoking marijuana two to five times per day on the days when they used marijuana. The highest reported use of marijuana by one woman was 10 times per day, every day throughout pregnancy to alleviate nausea.

Twelve (15%) of the 80 mothers reported drinking 2 to 4 oz of alcohol per day in the month prior to conception. Ninety-eight percent of the women reported drinking less than ½ oz of alcohol per day during pregnancy. Alcohol consumption prior to and during pregnancy was effectively matched between the marijuana-exposed and unexposed groups (Table 3). Thirteen of the 80 women reported use of cocaine during pregnancy. Cocaine use was more prevalent among the marijuana users.

There were no discernible differences in neonatal status between the marijuana-exposed and unexposed groups (Table 4).

Clinical Assessment of the Photographs

The relationship between maternal use of marijuana in the first trimester of pregnancy and the clinical identification of FAS-like facial characteristics among the children is presented in Table 5. The likelihood of identifying FAS-like facial features among the marijuana-exposed and unexposed groups was essentially the same. Children exposed to marijuana in the first trimester were not more likely to be classified by the dysmorphologist as having FAS-like facial features (as assessed by χ^2). Two children in the marijuana-exposed group were classified as having a probable FAS-like face; the mothers of these children reported consuming 1 or 2 oz of alcohol per day in the month prior to conception. One child in the group unexposed to marijuana was classified as having a probable FAS-like face; the mother had a low AA score in the month prior to pregnancy (0.2 oz/d) but did report two episodes of binge drinking during pregnancy (consumption of five or more drinks per occasion). The lack of association between marijuana and FAS-like facial features was not attributable to differences in sex, race, or age between the two groups. Evaluation of the photographs for facial patterns unrelated to FAS identified a few children with isolated, unusual features but failed to find any consistent patterns that differentiated the marijuana-exposed from the unexposed children.

In contrast, when the 80 children were stratified according to their mother's reported use of alcohol in the month prior to conception, the presence of thin upper lips and somewhat flat philtrums increased in frequency (although not significantly so) with increasing fetal exposure to alcohol (Table 5). It should be noted that maternal use of alcohol in this study population was relatively low compared to the levels of alcohol consumption that have previously been associated with FAS facial features in children. Fetal alcohol syndrome facial alterations have previously been associated with maternal consumption of at least 4 oz of alcohol per day[4,25]; only one child in the current study was exposed to this level of maternal consumption. No child was classified by the dysmor-

TABLE 2. Selected Characteristics of Women Who Did and Did Not Use Marijuana During the First Trimester of Pregnancy*

Characteristic	Marijuana	
	Unexposed (n = 40)	Exposed (n = 40)
Child's race (parent's race)		
White (white)	37	35
White (Oriental)	0	1
White (Chicano)	1	0
White (Native American)	0	1
White (other)	1	0
Black (black)	1	3
Child's age when photographed, y	6.3 (4.9–7.5)	6.3 (5.0–7.4)
Marital status		
Married	37	31
Yearly income†		
<$10 000	1	9
$10 000–$24 999	10	14
>$25 000	27	14
Unknown	2	3
Mother's age at child's birth,‡ y	30.7 (22–48)	26.9 (17–35)
Previous therapeutic abortions‡	0.2 (0–2)	0.7 (0–3)
Previous spontaneous abortions		
1st trimester	0.3 (0–4)	0.2 (0–4)
2nd trimester	0	0.05 (0–2)
Previous stillbirths	0.05 (0–1)	0
No. of pregnancies	2.5 (1–6)	2.6 (1–11)
Mother's education†		
Did not finish high school	0	6
Finished high school only	11	16
Attended college	29	18

* Values represent number or mean (range).
† Significance levels for difference within categories between exposed and unexposed were calculated with χ^2 without Yates' correction: $P < .01$.
‡ Significance levels for difference in means between exposed and unexposed were calculated by t test: $P < .01$.

phologist as having a definite FAS-like face. The proportion of children classified as having a "probable" FAS-like face increased with increasing maternal consumption of alcohol, but the increase was subtle and could have occurred by chance. Marijuana and cocaine use were equally distributed among the women who reported consuming less than 2 oz of alcohol per day prior to pregnancy and the women who reported consuming 2 oz or more per day.

Computerized Morphometric Assessment of the Photographs

In the present study, the shapes of triangles 1-4-12, 22-14-19, and 23-14-19 (previously found to be associated with prenatal alcohol exposure) did not differentiate, to a statistically significant degree, the children exposed to marijuana during the first trimester from the children with no reported exposure to marijuana during gestation. This lack of association persisted even when the exposed group was restricted to those exposed every day. In addition, we were unable to identify any triangles or patterns of minor abnomalies, not previously related to FAS, that differentiated the marijuana-exposed group from the unexposed group. The apparent lack of association between fetal marijuana exposure and facial dysmorphology in this study was not attributable to differences in sex, race, or age between the exposed and unexposed groups.

Shape differences in two of the three triangles previously associated with fetal alcohol exposure[4] were significantly associated with maternal consumption of alcohol in the month prior to conception *among the male children* in this study. It should be noted that in the present study population, alcohol and cocaine exposure was higher among the boys than the girls (Table 6). The sex of the child was also strongly correlated with facial size in this study population. As a result, it was necessary to perform the computerized morphometric assessment separately on the boys and girls. Upon doing so, the mean shape coordinates associated with triangles 22-14-19 and 19-23-14 were found to differentiate boys whose mothers reported consuming ≥ 2 oz of alcohol per day in the month prior to conception (n = 10) from boys exposed to lower levels of alcohol (n = 38) at modest significance levels ($T^2 = 6.65$, $P = .048$ and $T^2 = 6.33$, $P = .054$, respectively) (Fig 5). The tensor axes for this deformation suggested that boys with higher exposure to alcohol had relatively shorter midfaces. This finding was also evident in the measures of midface height recorded directly from the photographs (Table 7). The size of the study population was too small to stratify the alcohol results by marijuana exposure and perform formal tests of significance. Identification of the marijuana-exposed cases on the scatterplot of shape coordinates did, however, confirm that marijuana exposure was not confounding the apparent alcohol effect.

The shape of triangle 23-21-22 also differentiated the boys whose mothers reported consuming 2 to 4 oz of alcohol per day in the month prior to conception

TABLE 3. Other Drug Use Among the Women Who Did and Did Not Use Marijuana During the First Trimester of Pregnancy*

Characteristic	Marijuana	
	Unexposed (n = 40)	Exposed (n = 40)
Trimesters when marijuana was used		
1st only	0	11
1st and 2nd only	0	3
1st and 3rd only	0	2
All three	0	24
Frequency of marijuana use		
1–2 times/wk	0	15
3–4 times/wk	0	11
Every day	0	14
No. of joints smoked per occasion		
1	0	25
2–5	0	14
10	0	1
Trimesters when cocaine was used†		
Never	38	29
1st only	2	7
1st and 2nd only	0	1
1st and 3rd only	0	1
1st, 2nd, and 3rd	0	1
3rd only	0	1
Frequency of cocaine use†		
Never	38	29
<1 time/mo	2	8
1 time/mo	0	1
2–3 times/mo	0	2
No. of times cocaine was used per occasion during pregnancy†		
Never	38	29
1–3	2	9
4–6	0	2
Smoked cigarettes during pregnancy	12	26
No. of cigarettes smoked per day‡		
0	28	14
1–10	6	11
11–20	6	11
21–40	0	4
Average mg of nicotine per day among smokers	6 (0–22)	11 (0–40)
Average oz of alcohol per day in the month before pregnancy (AA score)	0.7 (0–2.0)	0.8 (.01–4.0)
Average oz of alcohol per day during pregnancy (AA score)	0.1 (0–1.0)	0.1 (0–1.0)

* Values represent number of subjects or the mean (range) of the outcome variable.
† Significance levels for differences within the collapsed categories (ever vs never) between exposed and unexposed was calculated using χ^2 without Yates' correction: $P < .01$.
‡ Significance level for difference within categories between exposed and unexposed was calculated using χ^2 without Yates' correction: $P = .009$.

(n = 10) from the boys whose mothers consumed less than 2 oz per day (n = 38) ($T^2 = 10.02$, $P = .01$) (Fig 6). The deformation in the triangle suggested that higher alcohol exposure was associated with retrognathia.

Triangle 22-14-17 (Fig 7) also differentiated the boys whose mothers reported consuming ≥ 2 oz of alcohol per day in the month prior to conception (n = 10) from the boys exposed to less than 2 oz of alcohol per day (n = 38) ($T^2 = 7.92$, $P = .028$). The direction of deformation in this triangle suggested that relative nose lengths were shorter among the boys exposed to higher levels of alcohol. This triangle did not differentiate between the girls with comparable exposures. This finding was corroborated in the distance measures taken directly from the photographs of all 80 children. When nose length, measured directly from the photographs, was regressed on ounces of alcohol consumed per day in the month prior to conception, a significant inverse relationship was noted (Table 7). The sex of the child also influenced nose length, with boys having longer noses than girls. An interaction term between sex and alcohol suggested that the effect of alcohol on nose length differed among the boys and the girls, which is consistent with the results of the digitized analysis of triangle 22-14-17.

Only 2 of the 32 mothers of girls reported consuming 2 oz or more of alcohol per day in the month prior to conception. Although shape changes were not apparent in our analyses of triangles, the sample size was far too small to draw conclusions.

The tensor axes in Figs 5, 6, and 7 appear similarly oriented. A biorthogonal grid was constructed using mean coordinates of lateral landmarks 14 through 23 to summarize the deformational contrasts between the 10 boys whose mothers reported consuming ≥ 2 oz of alcohol/day in the month prior to conception and the 38 boys with less exposure (Fig 8, A). The change in mean shape, as depicted by the biorthogonal grid, describes a shortening of the midface region, especially along the upper midline and retrusion of the chin, relative to the baseline 14-23. The shifts in the 10 mean landmarks between the exposed

TABLE 4. Birth Outcomes Among the Infants Whose Mothers Did and Did Not Use Marijuana During the First Trimester of Pregnancy*

Infant Characteristics	Marijuana	
	Unexposed (n = 40)	Exposed (n = 40)
Child's sex		
Female	15†	17
Gestational age		
<36 wk	0	2
36–42 wk	39	36
>42 wk	1	1
Unknown	0	1
Birth weight		
<2500 g	0	2
2500–4000 g	33	32
>4000 g	7	5
Unknown	0	1
Gestational age, wk	40.0 (36–43)	39.3 (32–43)
Body length, cm	51.1 (46–54)	50.2 (45–56)
Head circumference, cm	34.7 (31–39)	34.2 (31–38)
Apgar score (1 min)		
<7	4	4
7–10	36	35
Unknown	0	1
Apgar score (5 min)		
<7	0	0
7–10	40	39
Unknown	0	1

* Values represent number of subjects or mean (range).
† Group-matched to the exposed group.

and unexposed groups were parallel and for the most part had magnitudes proportional to their mean distances from the baseline (14-23) as would be expected if the overall shape change between groups was linear (or homogeneous) (Fig 8, B).[19] A significant linear shape change across all 10 landmarks was confirmed (F statistic on 2 and 31 *df* = 4.96, *P* = .013). In addition, an F statistic for nonlinearity was computed (F = 1.08 on 14 and 33 *df*, *P* = .40) confirming that the transformation across all triangles was adequately described by a simple (linear) global model. In other words, the directions of expansion and contraction were relatively consistent across all triangles mapped within the boundaries of these 10 landmarks. The linear component of this model explained 50% of the shape change between the two groups.

In the process of evaluating exposure to cocaine as a potential confounder for the facial patterns associated with alcohol exposure, patterns of facial anomalies associated with cocaine exposure were revealed. The mean shape coordinates associated with triangles 23-14-19, 23-14-17, and 23-14-22, all reflecting midface flattening or retrusion, were found to differentiate boys exposed to cocaine during the first trimester (n = 9) from the boys with no exposure to cocaine during pregnancy (n = 38) at modest significance levels (T^2 = 6.44, *P* = .053; T^2 = 8.78, *P* = .019; T^2 = 7.91, *P* =.028, respectively) (Fig 9). Exposure to cocaine on three or more days throughout gestation

TABLE 6. Gestational Exposure to Alcohol and Cocaine Among the Girls and Boys*

Maternal Drug Use	Girls (n = 32)	Boys (n = 48)
Alcohol (oz/d absolute alcohol)		
Month before conception		
0–0.9	18 (56)	24 (50)
1.0–1.9	12 (38)	14 (29)
2.0–4.0	2 (6)	10 (21)
During pregnancy		
0–0.5	32 (100)	46 (96)
1.0	0 (0)	2 (4)
Cocaine (days of use)†		
During pregnancy		
0	29 (91)	38 (79)
1–3	3 (9)	9 (19)
27	0 (0)	1 (2)

* Values represent number of subjects (percent).
† The male-female ratio among the cocaine-exposed group (10 [77%] of 13) is significantly different from an expected 50% (*t* test: *t* = 2.21, *P* = .047).

TABLE 5. Frequency of Fetal Alcohol Syndrome (FAS)-like Facial Characteristics Associated With Maternal Use of Marijuana in the First Trimester of Pregnancy and Alcohol Consumption 1 Month Prior to Conception*

Child's Facial Characteristics	Marijuana		Alcohol†		
	Unexposed (n = 40)	Exposed (n = 40)	0–0.9 (n = 42)	1–1.9 (n = 26)	2–4 (n = 12)
Midface					
Not flat	70	65	67	73	58
Somewhat flat	20	33	28	23	25
Definitely flat	10	2	5	4	17
Philtrum					
Not flat	90	85	93	81	83
Somewhat flat	10	5	7	19	17
Definitely flat	0	0	0	0	0
Upper lip					
Not thin	78	75	81	73	68
Somewhat thin	15	12.5	12	15	16
Definitely thin	7	12.5	7	12	16
Classification of overall facial appearance by dysmorphologist					
No unusual features	85	83	91	80	67
Unusual features, but not FAS-like face	10	10	5	12	25
Possible FAS-like face	2.5	2	2	4	0
Probable FAS-like face	2.5	5	2	4	8
Definite FAS-like face	0	0	0	0	0

* Values represent the proportion of children with the specified facial characteristic.
† AA score: ounces of absolute alcohol per day.

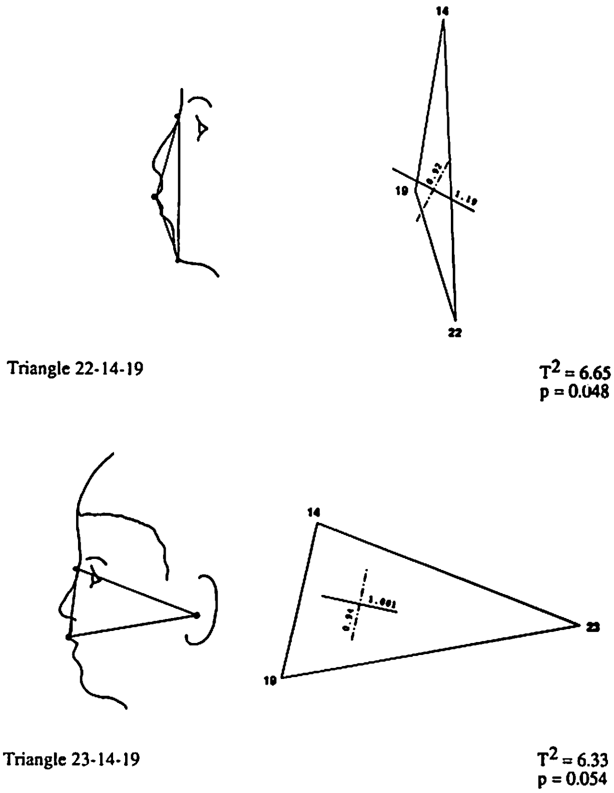

Fig. 5. Two lateral triangles (22-14-19 and 23-14-19) that were found to be associated with prenatal alcohol exposure in a previous study[4] were also found to be associated with fetal alcohol exposure among the boys in the current study. Boys whose mothers reported consuming ≥ 2 oz alcohol/day in the month prior to conception (n = 10) are contrasted with boys whose mothers reported lower alcohol consumption (n = 38).

in 4 boys was associated with increased intercanthal distance relative to palpebral fissure length when compared with the 44 boys with less or no exposure to cocaine (T^2 = 11.6, P = .0065). Three of these 4 boys received 3 to 9 days of exposure in the first trimester. No associations were observed among the three girls, all of whom were exposed to cocaine only once, in the first trimester. Separate analyses were performed for boys and girls because, as with the alcohol exposure, cocaine exposure was higher among the boys (Table 6) and the sex of the child was strongly associated with facial size. The effects associated with cocaine exposure were not attributable to variation in alcohol, marijuana, or tobacco exposure. The cocaine associations revealed in the landmark analyses were corroborated by the distance measures taken directly from the photographs.

DISCUSSION

In the current study, fetal marijuana exposure was not found to be associated, to a statistically significant extent, with facial features compatible with FAS. A few epidemiologic and clinical studies, however, have presented evidence suggesting an association between prenatal marijuana exposure and the presence of congenital malformations[26–31] or more specifically, features compatible with FAS.[3,4] The inconclusive nature of these reports can be attributed to one or more of the following factors: weak diagnostic sensitivity, questionable reliability of exposure, inadequate sample size, and/or strongly correlated covariates.

Only one of those studies, to our knowledge, reported a significant association between FAS-like facial features and maternal use of marijuana during pregnancy. In that prospective cohort study of 1690 mother-infant pairs, Hingson et al[2] reported that women who smoked marijuana during pregnancy were five times more likely than nonusers (95% confidence interval = 2.0 to 12; P = .001) to deliver a child with FAS-like features. The newborns were examined at 2 to 3 days of age by one of four pediatricians who then completed an anomaly checklist. The authors noted that marijuana use in their study population was strongly correlated with alcohol use. The authors also noted that children of women who averaged two or more drinks daily were not more likely to have FAS-like features when compared with children of women who reported no use of alcohol. Their reported lack of association between FAS-like features and maternal consumption of two to four drinks per day is consistent with other clinical studies. Fetal alcohol syndrome-like features are typically associated with chronic maternal alcoholism.[4] Combining the group that reported consuming two to three drinks per day with the group that reported consuming four or more drinks per day may have weakened the association with FAS-like features. In our digitized analysis of facial form, boys whose mothers reported consuming four or more drinks per day (2 oz or more of alcohol per day) prior to concep-

TABLE 7. Regression of Nose Length and Midface Height Measured Directly From the Photographs of All 80 Children on Sex and Maternal Consumption of Alcohol in the Month Prior to Conception

Variable	b	SE of b	β	F	Sig F
Midface height (entrocanthion to upper lip)*					
AAMB†	−.09	.05	−.18	3.0	.085
Sex‡	−.25	.08	−.36	11.7	.001
(Constant)	5.5	.07		6418.4	.0000
Nose length (entrocanthion to subnasale)§					
AAMB†	−.07	.02	−.43	8.5	.005
Sex‡	−.09	.04	−.41	7.1	.009
Sex × AAMB	.08	.04	.41	5.4	.023
(Constant)	1.69	.03		4131.4	.0000

* r^2 = .15, F = 6.7, P = .002, N = 80.
† AAMB, absolute ounces of alcohol per day in the month prior to conception.
‡ Sex: male = 0, female = 1.
§ r^2 = .12, F = 3.4, P = .022, N = 80.

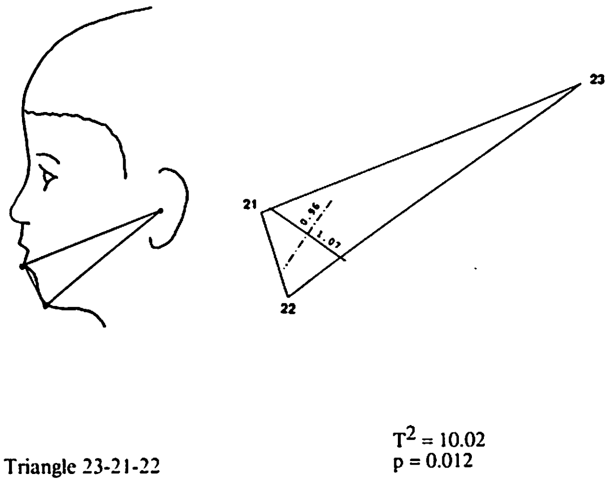

Fig. 6. Retrognathia associated with prenatal alcohol exposure in boys. Boys whose mothers reported consuming $\geq$ 2 oz alcohol/day in the month prior to conception (n = 10) are contrasted with boys whose mothers reported lower alcohol consumption (n = 38).

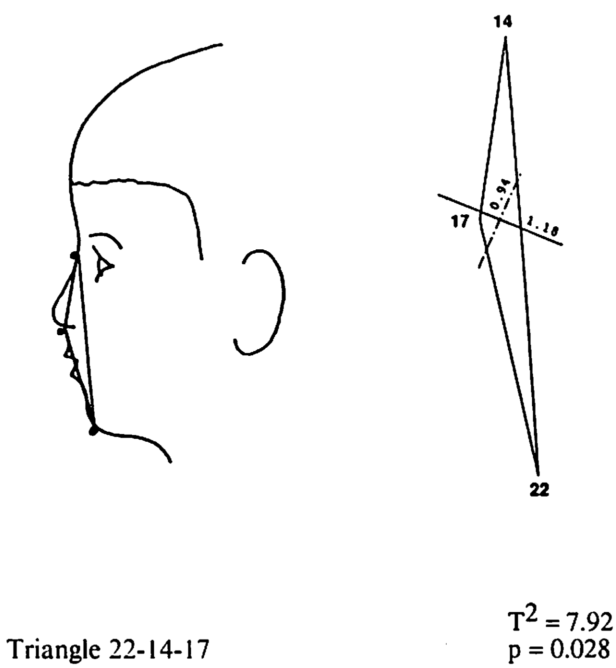

Fig. 7. Relative decrease in nose length associated with prenatal alcohol exposure in boys. Boys whose mothers reported consuming $\geq$ 2 oz alcohol/day in the month prior to conception (n = 10) are contrasted with boys whose mothers reported lower alcohol consumption (n = 38).

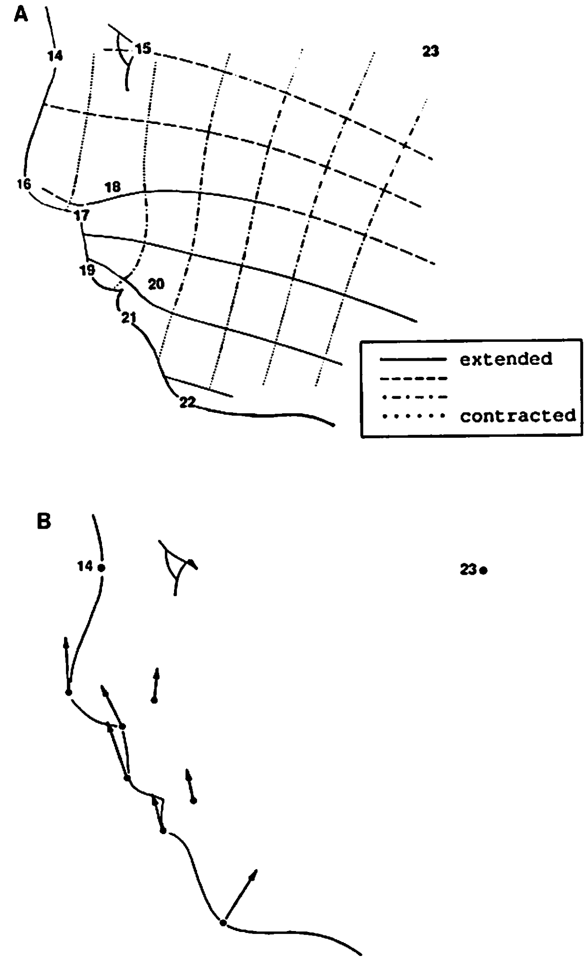

Fig. 8. A, Biorthogonal grid depicting the difference in mean shape between the 10 boys exposed to maternal alcohol consumption of 2 oz or more per day early in pregnancy and the 48 boys exposed to lower levels of maternal alcohol consumption. The grid describes a shortening of the midface region and retrusion of the chin relative to the baseline 14-23. B, Observed shift in the 10 mean lateral landmarks between the exposed and unexposed groups relative to the baseline 23-14.

tion were significantly different from those exposed to lower levels. When the women who reported consuming two drinks per day (1 oz of alcohol) were combined with those who consumed four or more drinks per day, the differences between the two exposure groups ($<$2 compared with $\geq$2 drinks) were no longer significant.

In the current study, maternal consumption of as little as 2 oz of alcohol per day, very early in gestation, was associated with FAS-like facial features. Fetal alcohol syndrome-like facial features were not associated with our measures of maternal use of alcohol during pregnancy. Reported use of alcohol during pregnancy was very low in this study population and was comparable in the marijuana-exposed and unexposed groups. Previous studies have suggested that reported use of alcohol in the month prior to conception is a better estimate of the mother's true alcohol consumption during the first 6 to 8 weeks of pregnancy, prior to confirmation of pregnancy. It is during this time period that facial development is most susceptible to teratogens.[32,33]

The deformations depicted by triangles 22-14-19, 22-14-17, 23-14-19, and 23-21-22 and the distance measures recorded directly from the photographs suggested that the children with higher alcohol exposure had shorter noses relative to midface height and were retrognathic. Both of these features are consistent with the FAS facial phenotype. In the current study, the triangular deformations and the distance measures taken directly from the photographs also confirmed that midface length was shorter among the children with higher alcohol exposure. In the literature, the midface is often described as being long relative to the nose. In this study, because all photo-

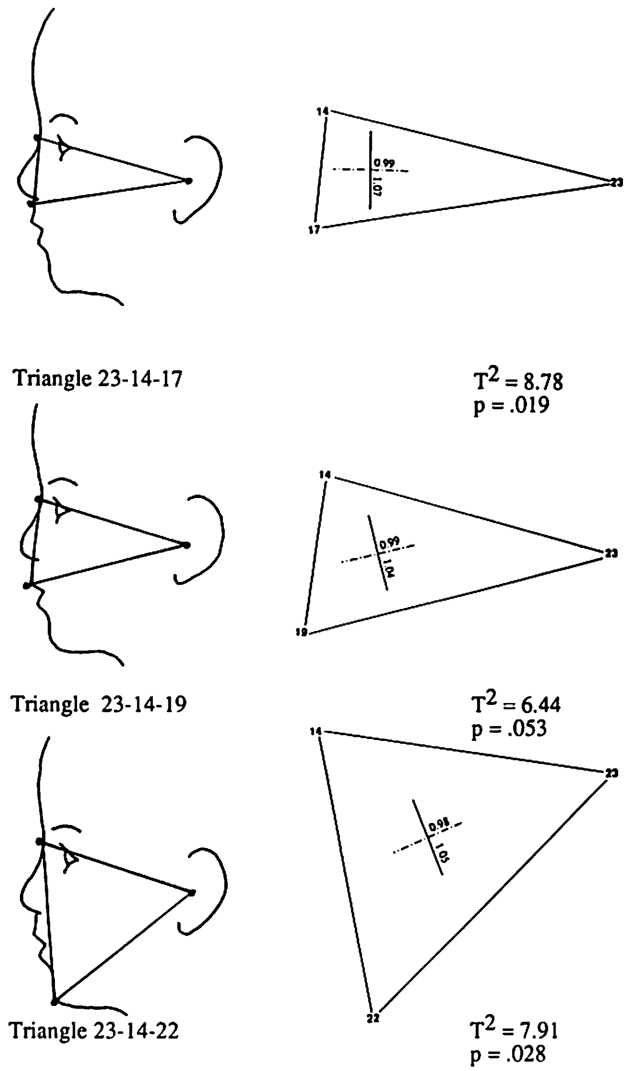

Fig. 9. Midface retrusion associated with first-trimester fetal cocaine exposure among boys. Boys with 1 to 9 days of first-trimester cocaine exposure (n = 9) are contrasted with boys with no cocaine exposure (n = 38).

graphs incorporated a measure of scale, we were able to record real measures of size across all photographs. It appeared that both nose length and midface height decreased with increasing alcohol exposure. In the boys, the mean nose lengths decreased from 3.53 cm to 3.42 cm to 3.25 cm as maternal alcohol consumption increased from (0 to 0.9) to (1 to 1.9) to (2 to 4) oz/d. Correspondingly, mean midface length decreased from 5.51 cm to 5.44 cm to 5.21 cm within each group.

Although triangles 22-14-19 and 23-14-19 were predictive of alcohol exposure in both the current study and the previous study by Clarren and colleagues,[4] it should be noted that the description of shape change for these triangles, as depicted by the directions of the tensor axes, differed. Direct comparisons between the "affected" groups in the two studies cannot be made because of differences in race, sex, and level of alcohol exposure. In the previous study, the group of eight children, among whom significant shape changes were detected, were exposed to 4 oz or more of alcohol per day, were 75% black, and consisted of both boys and girls. A permutation test was used to confirm that there was a significant shape change in these two triangles attributable to ethanol exposure and not to racial differences.

In contrast, in the present study, the group of 10 children among whom significant shape changes were found were exposed to only 2 to 4 oz of alcohol per day and were all boys, and only 10% were black. The shapes of triangles 22-14-19 and 23-14-19 were significantly different between blacks and whites, independent of alcohol exposure. The directions of the tensor axes, attributable to race, roughly match those attributed to alcohol in the previous study. In the current study these two triangles also identify significant contrasts between alcohol-exposed and unexposed groups, independent of race. To determine whether the direction of deformation attributable to alcohol seen in this predominantly white population is the same among a black population, a study sample of exposed and unexposed blacks will need to be assessed.

Two limitations in this study that could have contributed to a false-negative association between marijuana and FAS-like facial features were the reliability of reported drug use and lack of information on use of marijuana in the month prior to conception. Both of these limitations may have resulted in an underestimation of marijuana exposure. In the original prospective study, laboratory drug testing was not performed on all study participants. Instead, validity of self-reported drug use was investigated in a pilot study that preceded the original study. Self-reported drug use was compared to laboratory tests of drug levels present in body fluids in a random sample of 108 postpartum women. The proportion of questionable self-reports ranged from 0% to 3% depending on the drug.[8] These results are encouraging and probably suggest that if drug use has been underreported in this study population, it is unlikely to account for the complete lack of association found between marijuana exposure and FAS-like facial features. Estimating marijuana exposure during the first few weeks of gestation from reports of first trimester use may also have underestimated exposure. Prepregnancy levels of maternal marijuana use may have provided more accurate estimates of fetal exposure in the first 6 to 8 weeks when women are often unaware of their pregnancies. Although actual use of marijuana during the period of facial organogenesis will remain unknown in this study population, a study by Fried and colleagues[34] did find that of three "soft drugs" used by pregnant women (alcohol, nicotine, and marijuana), marijuana use by heavy users was the least reduced between prepregnancy and the first trimester.

To our knowledge, facial alterations associated with fetal cocaine exposure have not been previously reported. The teratogenic potential of cocaine has been documented in both the human[35-37] and animal literature,[38] but contrasting reports do exist.[39-43] Variations in the level and timing of exposure and differences in species susceptibility make it difficult to draw conclusions at this time.

The changes in facial form associated with cocaine exposure in our study population were subtle. Fetal cocaine exposure in this population was associated with increased intercanthal distance and increased midface retrusion. For all practical purposes, these findings would have gone unnoticed. The results should be interpreted cautiously. One cannot infer from the results presented here that fetal cocaine exposure adversely affects craniofacial development. Larger, prospectively designed studies will be required to substantiate these preliminary findings. In light of the prevalence of cocaine use among pregnant women, these preliminary findings strongly support the need for further investigation.

In summary, no dysmorphic facial anomalies were found associated with maternal marijuana use during the first trimester. Several methodologic aspects of this study lend credence to these results. The most sensitive period for the induction of facial malformations lies between the 2nd and 12th weeks of embryonic development.[33] The population we studied received relatively heavy exposure to marijuana during this vulnerable time period. Information on marijuana, alcohol, tobacco, and other drug use during pregnancy was collected prospectively in personal interviews conducted at 1 month postpartum, and the correlation between maternal alcohol and marijuana use during pregnancy was effectively eliminated by group-matching. On the other hand, facial features compatible with FAS were associated with maternal consumption of alcohol in the month prior to conception, substantiating the sensitivity of this diagnostic approach in identifying established syndromal features, even in a relatively small sample.

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