Minor Physical Anomalies are not Increased in the Offspring of Mothers with SLE
Concise Report
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Acknowledgments: This work was supported by NIH grants AR 41607, AR 30692, AR 48098, and K24 002138; an Arthritis Foundation Clinical Science Grant, the Lupus Foundation Western Pennsylvania and Illinois Chapters; and the Arthritis Foundation Western Pennsylvania and Illinois Chapters. We thank Bonnie Booher and Catherine Roukous for performing the infant examinations. We are indebted to Emily Wolf for her editorial assistance.

Key words: SLE, pregnancy, minor physical anomalies

Running title: minor physical anomalies not increased in offspring of mothers with SLE

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Abstract

Objective: In the general population, 1 or more minor physical anomalies (MPAs) occur in 14 to 40 percent of newborn infants. Our goal was to describe the frequency and type of MPAs in infants born to mothers with systemic lupus erythematosus (SLE).

Methods: Each trimester, pregnant women with SLE were assessed for disease activity, prescribed medication use, and exposures to tobacco, alcohol, and illicit drugs via a self-reported questionnaire. Infant exams were performed on 30 of 39 (77%) live births in SLE women. The frequency of MPAs was determined for each patient according to structured examination.

Results: The frequency of MPAs was as follows: two of the 30 subjects (7%) had three or more minor physical anomalies; four (13%) had two; seven (23%) had one; and 17 (57%) had none. One in three women reported alcohol, tobacco, and illicit drug use. Facial anomalies similar to those reported in Fetal Alcohol Syndrome were the most common MPAs reported. The relative risk (RR) and 95% confidence interval (CI) of any MPA was 2.05 (0.99-4.26) for tobacco use; 1.95 (0.92-4.11) for alcohol use; 1.36 (0.165-11.23) for maternal disease flare; 0.63 (0.27-1.47) for prednisone use; and 0.72 (0.21-2.44) for aspirin use.

Conclusion: In this study, 13 of 30 (43%) infants had minor anomalies consistent with the range of rates reported in the general population. Counseling for preventable self-reported exposures such as alcohol consumption is advisable in addition to monitoring for SLE-related maternal concerns.
Congenital anomalies present at birth are classified as major or minor [1]. Major anomalies such as a cleft lip are easily identified; however, minor physical anomalies (MPAs) are often overlooked [2]. MPAs are found in variable body areas such as the face and hands [2]. In some ethnic or racial groups, certain minor features such as clinodactyly of the fifth finger can be familial and considered a normal phenotypic variant [2]. The occurrence of at least one MPA without an associated major anomaly is estimated in the range from 14 to 40 percent of all healthy newborn infants [3].

Pregnant women with lupus often inquire if their baby is at risk for congenital anomalies. Most of the available information describes the occurrence of and risk factors for preterm birth, miscarriage, stillbirth, intrauterine growth restriction, and preeclampsia [4]. However, little is known about the presence of major or minor anomalies in infants born to women with lupus. The aim of this study was to determine the frequency and type of MPAs in the newborns of women with SLE.

Patients and Methods

This study included 44 pregnant women with lupus followed prospectively at the University of Pittsburgh between January 1, 1991 and December 31, 1994. Written informed consent was obtained from each study subject. Each trimester, participants were assessed for disease activity using the modified Systemic Lupus Activity Measure (mSLAM) [5]. Their use of prescription medication (prednisone, hydroxychloroquine, heparin, aspirin, and anti-hypertensives), tobacco, alcohol, and illicit drugs (cocaine, amphetamines, and marijuana) was obtained via a self-reported questionnaire. Examinations performed on infants between 1 to 245 days of age included morphologic assessments and were conducted according to a specified protocol by study nurses trained to ensure standard measurement reliability, which was checked on a monthly basis. MPAs were those defined by Smith [6]. Standardized techniques were used to measure weight and crown-to-heel length.

Definitions

Maternal disease activity, as assessed by the mSLAM, excludes weight loss and erythrocyte sedimentation rate (ESR) [5]. Active disease or flare was defined as mSLAM ≥7 and inactive disease as mSLAM <7 [7].

Fetal outcomes were defined as follows: full-term birth (≥37 weeks gestation); preterm birth (<37 weeks gestation); spontaneous abortion (spontaneous termination of pregnancy < 20 weeks gestation); stillbirth (spontaneous termination of pregnancy > 20 weeks gestation); and small for gestational age (SGA) (birth weight < 10th percentile for the stated gestation) [8]. Descriptive statistics were used to describe maternal and fetal outcomes, maternal disease activity, prescription medication use, and self-reported behavioral exposures. Frequencies of MPAs were determined for each patient. The presence of at least one MPA versus no MPAs served as the dependent, binary variable. Prescribed medication use and self-reported behavioral exposures (tobacco, alcohol, and illicit drug use) were examined as predictors of at least one MPA. The Mantel-Haentzel method was used to estimate the crude relative risks (RR) and 95% confidence intervals (CI) and to describe the strength of the association between the presence of at least one MPA and prescribed medications, self-reported behavioral exposures, and maternal disease flare.
Results

Of the 44 pregnancies, 39 (89%) were live births. The 5 (11%) fetuses who did not survive included 2 (5%) spontaneous abortions and 3 (7%) stillbirths. Infant examinations were performed on 30 of 39 (77%) live births. Every attempt was made to examine all infants including one evaluation performed 245 days after birth. However, 9 infant examinations were not conducted due to scheduling difficulties.

For the 30 pregnant women with lupus whose infants were examined, the mean age at lupus diagnosis was 22.8 (SD ±5.7) years and the mean age at delivery was 28.3 (SD ±4.3) years. The mean duration of pregnancy was 38.2 (SD ±2.3) weeks. The self-reported race was 25 (83%) Caucasian and 5 (17%) African-American. There were no differences in demographics between the mothers whose infants had and did not have examinations (data not shown).

Twenty-two (73%) of the 30 infants were full-term births, 6 (20%) were preterm births (one infant born at 31, 32, 25 weeks and three infants born at 36 weeks gestation), and 2 (7%) were SGA. There were 17 (56.6%) male and 13 (43.3%) female infants. The mean birth weight was 3.1 (SD ±0.6) kg and the mean length was 50.2 (SD ±6.8) cm. The mean head circumference calculated for the 13 (43.3%) infants examined within one week of their birth was 34.5 cm (SD ±2.0). There were no demographic differences in sex and mean birth weight between the infants who were and were not examined for MPAs (data not shown).

Seven of the 30 women whose offspring were examined for MPAs reported tobacco use, while four reported alcohol consumption, and two each reported amphetamine and marijuana use. Prescribed medication use during pregnancy in these women included prednisone (n=15), aspirin (n=6), and hydroxychloroquine (n=1). Mothers of infants not examined reported similar exposures including with one woman who used alcohol and amphetamines, while another mother used tobacco. The use of prescription medications including prednisone, aspirin, and hydroxychloroquine was similar between mothers whose infants were and were not examined (data not shown).

There were no major anomalies in any live infant examined or noted in the autopsy report available on one stillbirth. Two of 30 (7%) women delivered babies with ≥3 MPAs; 4 (13%) had 2; 7 (23%) had 1; and 17 (57%) had none.

Facial anomalies included a flat nasal bridge in five infants, hypoplastic nose in four, long philtrum in three, high arched palate in three, and thin vermillion, posterior rotated ears, low set ears, and protruding ears in one infant each. Limb anomalies included syndactyly in one infant, polydactyly in one, and length discrepancies in the second and third toes in two infants.

Maternal flare (mSLAM ≥7 at any visit) occurred in 4 women. In the infants of these women, two had no MPAs and two had one MPA each; however, the mothers whose infants had anomalies also reported amphetamine or marijuana use. The number of MPAs stratified by self-reported exposures and prescribed medications is shown in Table 1.

Crude relative risks (RR) and 95% confidence intervals (CI) for estimating the association between at least one MPA and maternal self-reported exposures or prescribed medication are shown in Table 1. In addition to the noted exposures, the association between disease flare and the presence of one or more MPAs was also estimated (RR 1.36; CI 0.17-11.23). No significant associations were found between any exposures, medications, or disease flare and at least one MPA in an infant of a mother with SLE. We were unable to calculate a RR for any illicit drug exposure because there were no reported maternal exposures in the infants without any MPAs.
Discussion

This study is the first to systematically assess infants for MPAs. The frequency of any MPA in an infant of a mother with lupus was 43%, which was consistent with rates in the general population [3].

Importantly, types of anomalies reported in our study mostly involved the face. Flat nasal bridge, hypoplastic nose, and long philtrum have been reported in infants with fetal alcohol exposure [6] and were found among infants of mothers who reported drinking alcohol during pregnancy (RR 1.95; CI 0.92-4.11). One third (10/30) of women whose infants were examined reported use of alcohol (13.3%), tobacco (23.3%), and/or illicit drugs (13.3%) during pregnancy and the proportion of substance use was similar in women (2/9) whose infants were not examined. These rates are consistent with reports of use among non-pregnant women with SLE [9] and while rates may vary, prior studies have indicated that approximately 22% of women in the general population report tobacco use during pregnancy [10], an estimated 20% consumed alcohol [10] [11], and 11% or less use marijuana and/or other substances [10] [11].

In this study, neither the exposure to prednisone or aspirin in utero nor the presence of maternal disease flare during pregnancy was associated with MPAs in infants born to mothers with lupus who were counseled specifically for lupus management during pregnancy.

Strengths of this study include documentation of exposure to medications and substance use, and the protocol design for the infant examinations where the nurses were blinded to the maternal self-reported exposures. However, there are several limitations in this study and one is the small sample size, which limits the statistical power. All self-reported behavioral exposures were recorded during pregnancy and prior to any infant examination, and 10/12 (83%) women reporting exposures to tobacco, alcohol or illicit drugs had their infants examined, minimizing selection bias as a potential limitation. We do not have information on the quantity of alcohol or illicit drugs consumed nor tobacco products used. Since patients were counseled to avoid alcohol, tobacco, and illicit drugs during pregnancy, we feel that any self-reported substance exposure is relevant.

Other limitations include our inability to examine all infants and the stillborn fetuses. However, maternal self-reported exposures and prescribed medication use were similar in the examined and unexamined infants. Finally, we are unable to comment on the long-term outcome of these infants, as they have not been re-examined.

The frequency of MPAs in these offspring of lupus mothers and the general population is similar [3]. In this small study, infants exposed to prednisone or aspirin in utero and whose mothers had a disease flare during pregnancy did not have an increased risk of at least one MPA. Our findings suggest that the potential risk factors for MPAs in this population were exposures to alcohol and tobacco. Although anomalies have clearly been attributed to alcohol, this is not the case for tobacco. However, women who smoke tobacco are more likely to drink alcohol and use illicit drugs and our sample size was not sufficient to differentiate between effects of these exposures. Our observations of multiple facial anomalies suggest the possibility of fetal alcohol effects. Therefore, counseling for substance use in addition to monitoring for lupus-related maternal concerns is recommended.
References
Table 1. Crude relative risk (RR) and 95% confidence interval (CI) estimating the association between maternal exposure and the presence of at least one Minor Physical Anomaly (MPA).

<table>
<thead>
<tr>
<th>Maternal Exposure</th>
<th>No.</th>
<th>%</th>
<th>No. of MPAs per Infant</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>0 (n=17**)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tobacco</td>
<td>7</td>
<td>23.3</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Alcohol</td>
<td>4</td>
<td>13.3</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Any illicit drug</td>
<td>4</td>
<td>13.3</td>
<td>0</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Prednisone†,††</td>
<td>15</td>
<td>50.0</td>
<td>10</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Aspirin‡‡</td>
<td>6</td>
<td>20.0</td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

*Mothers may have multiple exposures; therefore, totals for each column are not additive

**Number of infants

∞ Unable to calculate RR because this exposure was not reported in mothers whose infants did not have any MPAs

† Prednisone doses ranged from 2.5 mg to 80 mg daily and one woman was also on hydroxychloroquine

‡‡ Only medications used more than once included in these calculations