CONCISE REPORT

Minor physical anomalies are not increased in the offspring of mothers with systemic lupus erythematosus

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Objective: To determine the incidence and type of minor physical anomalies (MPAs) in infants born to mothers with systemic lupus erythematosus (SLE).

Methods: Each trimester, pregnant women with SLE were assessed for disease activity, prescribed drug use, and exposure to tobacco, alcohol, and illicit drugs through a self reported questionnaire. Infant examinations were performed on 30/39 (77%) live births in women with SLE and the incidence of MPAs determined.

Results: 2/30 (7%) patients had three or more MPAs; 4 (13%) had two; 7 (23%) had one; and 17 (57%) had none. One in three women reported alcohol, tobacco, and illicit drug use. Facial anomalies were the most common MPAs. The relative risk and 95% confidence interval for any MPA were 2.05 (0.99 to 4.26) for tobacco use; 1.95 (0.92 to 4.11) for alcohol use; 1.36 (0.165 to 11.23) for maternal disease flare; 0.63 (0.27 to 1.47) for prednisone use; and 0.72 (0.21 to 2.44) for aspirin use.

Conclusion: 13/30 (43%) infants had minor anomalies—a similar incidence to that of the general population. Counselling for preventable self reported exposure is advisable in addition to counselling specifically for lupus management during pregnancy.

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 various 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 to be in the range from 14 to 40% 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 pre-eclampsia.[4] However, little is known about the presence of major or minor anomalies in infants born to women with lupus. This study aimed at determining the incidence and type of MPAs in the newborns of women with systemic lupus erythematosus (SLE).

PATIENTS AND METHODS

Forty four pregnant women with lupus followed up prospectively at the University of Pittsburgh between 1 January 1 1991 and 31 December 1994 were studied. 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 drug (prednisone, hydroxychloroquine, heparin, aspirin, and anti-hypertensive drugs), tobacco, alcohol, and illicit drugs (cocaine, amphetamines, and marijuana) was obtained through a self reported questionnaire. Examinations performed on infants between 1 and 245 days of age included morphological assessments and were conducted according to a specified protocol by study nurses trained to ensure standard measurement reliability, which was checked monthly. MPAs were those defined by Smith.[6] Standardised 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.[5] Active disease or flare was defined as an mSLAM $\geqslant 7$ and inactive disease as an mSLAM <7.[7]

Fetal outcomes were defined as follows: full term birth ($\geqslant$37 weeks' gestation); preterm birth ($<$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 (birth weight $<$10th centile for the stated gestation).[8] Descriptive statistics were used to describe maternal and fetal outcomes, maternal disease activity, prescription drug use, and self reported behavioural exposure. The incidence of MPAs was determined for each patient. The presence of at least one MPA versus no MPAs served as the dependent, binary variable. Prescribed drug use and self reported behavioural exposure (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 risk (RR) and 95% confidence interval (CI) and to describe the strength of the association between the presence of at least one MPA and prescribed drugs, self reported behavioural exposure, and maternal disease flare.

RESULTS

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

Abbreviations: CI, confidence interval; MPAs, minor physical anomalies; mSLAM, modified Systemic Lupus Activity Measure; RR, relative risk; SLE, systemic lupus erythematosus

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)

		No of MPAs per infant*				RR	95% CI
Maternal exposure	No (%)	0 (n = 17†)	1 (n = 7†)	2 (n = 4†)	⩾3 (n = 2†)		
Tobacco	7 (23)	2	2	1	2	2.05	0.99 to 4.26
Alcohol	4 (13)	1	1	1	1	1.95	0.92 to 4.11
Any illicit drug	4 (13)	0	3	1	0	‡	–
Prednisone§¶	15 (50)	10	2	2	1	0.63	0.27 to 1.47
Aspirin¶	6 (20)	4	1	1	0	0.72	0.21 to 2.44

*Mothers may have multiple exposure; 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 receiving hydroxychloroquine; ¶only drugs used more than once included in these calculations.

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

Twenty two (73%) of the 30 infants were full term births, six (20%) were preterm births (one infant each at 31, 32, 25 weeks and three infants born at 36 weeks' gestation), and two (7%) were small for gestational age. Of the 30 infants, 17 (57%) were male and 13 (43%) female. The mean (SD) birth weight was 3.1 (0.6) kg and the mean length 50.2 (6.8) cm. The mean (SD) head circumference calculated for the 13 (43%) infants examined within 1 week of their birth was 34.5 (2.0) cm. No demographic differences were found 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, four reported alcohol consumption, and two each reported amphetamine and marijuana use. Prescribed drug use during pregnancy in these women included prednisone (n = 15), aspirin (n = 6), and hydroxychloroquine (n = 1). Mothers of infants not examined reported similar exposure, including one woman who used alcohol and amphetamines, and another who used tobacco. The use of prescription drugs including prednisone, aspirin, and hydroxychloroquine was similar between mothers whose infants were and were not examined (data not shown).

No major anomalies were found in any live infant examined or noted in the necropsy report available for one stillbirth. Two of 30 (7%) women delivered babies with ⩾3 MPAs; four (13%) had two; seven (23%) had one; 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 four 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. Table 1 shows the number of MPAs stratified by self reported exposure and prescribed drugs.

In addition to the noted exposure, the association between disease flare and the presence of one or more MPAs was also estimated (RR = 1.36; 95% CI 0.17 to 11.23). No significant associations were found between any exposure, drugs, or disease flare and at least one MPA in an infant of a mother with SLE. We were unable to calculate an RR for any illicit drug exposure because there was no reported maternal exposure in the infants without any MPAs.

DISCUSSION

As far as we know, this study is the first systematically to assess infants for MPAs. The incidence of any MPA in an infant of a mother with lupus was 43%, which is consistent with the incidence 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; 95% CI 0.92 to 4.11). One third (10/30) of women whose infants were examined reported use of alcohol (13%), tobacco (23%), and/or illicit drugs (13%) 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 although rates may vary, prior studies have indicated that about 22% of women in the general population report tobacco use during pregnancy,[10] an estimated 20% consume alcohol,[10 11] and ⩽11% 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 counselled specifically for lupus management during pregnancy.

Strengths of this study include documentation of exposure to drugs and substance use, and the protocol design for the infant examinations where the nurses were unaware of the maternal self reported exposure. However, there are several limitations to this study and one is the small sample size, which limits the statistical power. All self reported behavioural exposure was recorded during pregnancy and before any infant examination, and 10/12 (83%) women reporting exposure to tobacco, alcohol, or illicit drugs had their infants examined, minimising selection bias as a potential limitation. We do not have information on the quantity of alcohol or illicit drugs consumed or on the tobacco products used. Because patients were counselled 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 exposure and prescribed drug 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 incidence 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 exposure 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 the effects of these exposures. Our observations of multiple facial anomalies suggest the possibility of fetal alcohol effects. Therefore, counselling for substance use in addition to monitoring for lupus related maternal concerns is recommended.

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