In utero azathioprine exposure and increased utilization of special educational services in children born to mothers with systemic lupus erythematosus

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ABSTRACT

Objective: Azathioprine (AZA) is recognized among immunosuppressive medications as relatively safe during pregnancy for women with systemic lupus erythematosus (SLE) requiring aggressive treatment. This pilot study aimed to determine whether SLE therapy during pregnancy was associated with developmental delays in offspring.

Methods: This cohort study included SLE patients with at least one live birth post-diagnosis. Medical histories were obtained via interviews and chart review. Multiple logistic regression was used to examine associations between SLE therapy during pregnancy and maternal report of special educational (SE) requirements (as proxy for developmental delays) among offspring. Propensity scoring (incorporating corticosteroid use, lupus flare, and lupus nephritis) was used to account for disease severity.

Results: Of 60 eligible offspring from 38 mothers, 15 required SE services, the most common indication for which was speech delay. 7 of the 13 (54%) children with *in utero* AZA exposure utilized SE services versus 8 of 47 (17%) non-exposed (p<0.05). After adjustment for pregnancy duration, small for gestational age, propensity score, maternal education and antiphospholipid antibody syndrome, AZA was significantly associated with SE utilization occurring from age 2 onward (OR 6.6, 95% CI 1.0, 43.3), and bordered significance for utilization at any age or age <2 years.

Conclusions: AZA exposure during SLE pregnancy was independently associated with increased SE utilization in offspring, after controlling for confounders. Further research is indicated to fully characterize developmental outcomes among offspring with *in utero* AZA exposure. Vigilance and early interventions for suspected developmental delays among exposed offspring may be warranted.

Significance and Innovations

- Azathioprine exposure during SLE pregnancy in this study was independently associated with increased requirement for special educational services among offspring, after controlling for suspected confounders.

- Increased vigilance and early intervention for suspected developmental delays among children born to mothers with SLE may be warranted, as early intervention is effective in improving long term functioning among affected children.

- Our findings do not establish sufficient risk that AZA should be withheld in lupus pregnancy requiring immunosuppressive therapy, as active, untreated disease may result in worse maternal and fetal outcomes.

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Systemic lupus erythematosus (SLE) is a multisystem, autoimmune disease associated with strong female preponderance and incidence that increases during the reproductive years[1,2]. . Due in large part to improved disease management, morbidity and mortality for SLE patients over the last several decades has decreased, providing more women with SLE the opportunity to achieve successful pregnancies[3].

Among immunomodulators used for SLE, azathioprine (AZA), hydroxychloroquine, cyclosporine and glucocorticoids are considered relatively safe for use during pregnancy[4], while others (cyclophosphamide, methotrexate, mycophenolate mofetil) are contraindicated, especially during the first two trimesters. However, little is known about long term effects on children born to mothers with SLE who were treated with these medications during pregnancy. Concerns have been raised that neurocognitive outcomes in these children may be influenced by maternal SLE disease activity and its treatment during pregnancy[5-10].

We performed this study to investigate potential risk factors for increased utilization of special educational (SE) services, as a proxy for developmental delays, among offspring of mothers with SLE, and in particular to identify novel associations with specific features of lupus or its treatment during pregnancy.

PATIENTS AND METHODS

Study population

Women attending rheumatology outpatient clinics at the University of Michigan, and participants in the Michigan Lupus Cohort (MLC), were enrolled between December 2008-November 2010. Patients were eligible if they met ≥4 American College of Rheumatology (ACR) criteria for SLE [11,12] prior to at least one pregnancy, and had at least one live birth following SLE diagnosis, with year of delivery occuring from 1993 onward. This research was approved by the University of Michigan Institutional Review Board; written informed consent was obtained from the mothers and assent or consent of the offspring was obtained for children aged 10-17 years old.

Data collection

Data were collected from the mothers through a structured interview with a study team member, as well as medical record review. The following information was obtained:

Maternal medical and obstetric history. Data including SLE disease duration, history of disease manifestations (*e.g.*, lupus nephritis, hypertension), and history of antiphospholipid antibody syndrome (APS) defined according to published criteria[12,13] were recorded. Medication exposures were recorded, including details on fluorinated and non-fluorinated corticosteroids (non-fluorinated considered high dose if average daily dose was >20mg for majority of pregnancy). An additional "significant steroid" variable was derived to combine exposures likely to cross the placenta into one category (>20 mg/d non-fluorinated steroids or fluorinated steroids)[13]. Laboratory profiles, including antiphospholipid antibodies and renal biopsies data were also recorded.

Childrens' medical and developmental history. Antenatal complications and delivery information, as well as medication use at conception and during pregnancy were recorded. Childrens' perinatal and pediatric general health histories were collected, including time spent in intensive care units, chronic medication exposures, frequency of infections (beyond typical childhood infections), and need for regular medical follow-up beyond pediatrician "well child" examinations. Small for gestational age (SGA) was defined as neonatal birth weight below the 10th percentile for gestational age, based on U.S. national reference data[14]. The primary outcome was maternal report of developmental delay or utilization of SE services due to any significant lag in a child's cognitive, physical or social maturity when compared with established age appropriate norms. Included in this definition were delays in language and hearing, or any special educational need prompting referral by the child's pediatrician or teacher for special educational services (*e.g.*, occupational or speech therapy, behavioral counseling, tutoring). In addition to collecting such data in open-ended fashion, we specifically collected data on attention deficit hyperactivity disorder (ADHD). Delays were categorized according to whether they occurred during the first two years of life, and/or from age 2 years onward.

Statistical analysis

Baseline summary statistics were computed as mean and standard deviation or median and interquartile range for continuous variables, and frequency and proportion for categorical variables. Non-parametric statistics were used if appropriate. Demographic characteristics of mothers among the groups with and without SE service utilization were assessed for

comparability. While the primary outcome was utilization of SE services occurring at any age during childhood, separate models were also examined according to SE requirement prior to age two years, and from age two years onward. We compared baseline characteristics (including maternal and perinatal variables) among those children with and without SE utilization using Fisher's exact and Wilcoxon rank-sum tests. Adjustment for multiple comparisons was made by Šidák-Holm's method[15,16]. Multivariable logistic regression was used to adjust for potential confounders. Variables judged to have clinical relevance based on *a priori* knowledge were retained in the final models regardless of significance.

Since AZA use implies a need to treat active disease and/or maintain remission after moderate to severe disease manifestations, we derived a propensity score to account for potential confounding by indication. Using multinomial logistic regression, we found the predicted probability of AZA treatment for each patient based on non-fluorinated corticosteroid dose during pregnancy, lupus nephritis (renal biopsy WHO Class III-V), and SLE flare during pregnancy. This predicted probability was then used as a covariate in the multivariable logistic models examining the association between AZA and SE utilization. Some mothers had more than one child included in the study; however, correlation was ignored in the primary results since the small sample size prohibited regression methods that take correlation into account. We therefore conducted sensitivity analyses, in which we ran a simulation on 1000 reduced samples that consisted of one randomly-selected child per mother, and examined the distribution of p-value from these models. Statistical analyses were performed in Stata 11.1 (StataCorp, College Station, TX)[17].

RESULTS

Eighty-five women were screened for the study, of whom 43 did not meet eligibility criteria, *e.g.*, because pregancies occurred prior SLE diagnosis, and 4 were excluded due to inability to obtain outcomes data. This analysis included data from the remaining 38 mothers and their 60 eligible offspring. Full medical records were available for 70% of the pregnancies. The median age (IQR) of the offspring at the time of data collection was 5.7 (3.4, 9.2) years. Maternal characteristics and SLE features are summarized in **Table 1**. There were no significant differences in maternal age, race or level of education for mothers of the children with versus without SE requirement (data not shown). Among the offspring, there were 56 singleton

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pregnancies, and two twin sets (delivered at 30 and 36 weeks; no SE utilization occurred in the twins). SE utilization was reported in 15 (25%) of the 60 children, with the most prevalent indication being speech delay (requiring speech therapy), in 12 of these 15 children. When categorized according to timing of delays, 10 of the 60 (17%) children received SE in the first two years of life, and 14 (23%) from age two onward; 9 children had SE requirement reported for both time periods. The reasons for SE utilization are enumerated in **Table 2**.

Maternal/fetal chracteristics among those requiring SE are presented in **Table 3**. Several suspected confounders, including small for gestational age and maternal education, were not detected in this population to be associated with SE utilization at any age in univariate analyses. However, antiphospholipid antibody syndrome was significantly associated with with SE utilization at any age, and from 2 years of age onward. Among maternal SLE therapeutics during pregnancy, corticosteroid dose and AZA were each associated in univariate analyses with a higher proportion of reported SE utilization among offspring with *in utero* exposure. When accounting for multiple comparisons, the adjusted p-value for AZA was p=0.08, whereas the adjusted value for non-fluorinated corticosteroids was p=0.4. The proportions of SE utlization according to *in utero* AZA exposure are presented in **Figure 1**. Overall, SE requirements were reported among 7 of 13 (54%) children with *in utero* AZA exposure versus 8 of 47(17%) without AZA exposure [univariate OR 5.69 (95% CI 1.50, 21.50); p<0.01]. In the first two years of life, 5 of the 13 (38%) children with *in utero* AZA exposure had SE requirement compared to 5 of 47 (11%) non-exposed children (p<0.05); from two years onward 7 of 12 (58%) children with exposure had SE requirement compared to 7 of 47 (15%) with no exposure (p<0.01).

Results from multivariable logistic regression models are presented in **Table 4**. When adjusting for pregnancy duration, SGA, maternal education level, and maternal APS (Model A), *in utero* AZA exposure was associated with significantly increased SE utilization at any age, and for both subgroups (age <2 or ≥2 years), with odds ratios (ORs) ranging from 6.1-10.0. When propensity score was added as a covariate (Model B), ORs for AZA were 4.4-6.6, with significance for SE utilization at age ≥2 years, and borderline significance for SE utilization at any age or <2 years (**Table 4**).

We performed a sensitivity analysis to account for potential correlation due to multiple births from the same mother, in which we ran a simulation on 1000 reduced samples that consisted of

one randomly-selected child per mother, modeling the outcome of SE utilization at any age (see methods). From this simulation of models including propensity score, 22% of the 1000 random samples were significant at alpha of 0.1, lending support to conclusions based on models using the full sample size of 60 children.

We performed a further sensitivity analysis restricted to the first-eligible offspring for each mother (n=38); to reduce the number of variables in this smaller model, we incorporated into the original propensity score the covariates from Model A. Results from this sensitivity analysis were consistent with those from our primary analyses, though not reaching statistical significance in this reduced subset of the population [OR 2.5 (95% CI 0.3, 21.7) for delay at age <2 years; OR 2.9 (95% CI 0.4, 19.4) for delay at age ≥2 years].

DISCUSSION

In this pilot study, we found an association between maternal AZA therapy during pregnancy and SE utilization, a proxy for developmental delays, in offspring (particularly after age 2 years). This association remained significant when adjusting for recognized risk factors for learning disorders, e.g, prematurity and low birth weight[18,19]. We did not find an increased risk for SE utilization among male offspring, as described in studies of dyslexia and learning delays among offspring of SLE mothers[5-9,20,21].

We controlled for dose of antenatal glucocorticoid exposure, both fluorinated and non-fluorinated. Fluorinated steroids (dexamethasone, betamethasone) cross the placenta, and have been linked to cognitive dysfunction in children after *in utero* exposure, including outside the setting of threatened premature delivery[22]. Only two offspring in our study were exposed to fluorinated steroids, precluding ability to focus on this mode of therapy. Non-fluorinated glucocorticoids cross the placenta at a much lower rate: fetal exposure is regulated by placental 11β-hydroxysteroid dehydrogenase which converts active cortisol into inactive cortisone[13]. Most likely, ~10% of non-fluorinated glucocorticoid crosses into the fetal circulation at doses of ≤20 mg[13,23]. While in univariate analyses dose of non-fluorinated steroids was associated with SE requirement, this was no longer significant when adjusting for multiple comparisons, nor in multivariable modeling (OR 1.04; 95% CI 0.95, 1.14).

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Our study population included women with a wide range of lupus activity, a significant number of whom required immunosuppressive, antimalarial and/or glucocorticoid therapy during their pregnancies. In the majority of cases, immunosuppressive therapy during pregnancy was with AZA (n=13). Two subjects had exposure to mycophenolate mofetil (MMF), one throughout first and second trimesters (prior to FDA Category D prescribing warning for MMF), and one at conception, at which time MMF was stopped. No other maternal characteristic, with the exception of APS, predicted SE requirement in children.

AZA has been used for over fifty years in solid organ transplantation and is used frequently for therapy of organ threatening autoimmune diseases. For SLE, AZA is considered both a steroid sparing agent and a "maintenance drug" for use after initial disease control is achieved with cyclophosphamide[24]. While AZA is considered relatively safe during pregnancy, it remains listed as a category "D" drug by the FDA, indicating that potential benefits may warrant its use in pregnant women despite potential risks. Studies of AZA and pregnancy outcomes from diverse patient populations (solid organ transplant, rheumatic disease, and inflammatory bowel disease) have revealed inconsistent results: there are case reports of malformations occurring in AZA treated women, as well as rare reports of fetal immunologic abnormalities, including newborn hypogammaglobulinemia and pancytopenias, most of which normalize by 10 weeks[25-29]. Some studies have reported increased rates of spontaneous abortions, prematurity, intrauterine fetal growth retardation and low birth weight, [27-29] but these studies often include patient populations with heterogenous and sometimes poorly controlled underlying diseases. Thus findings may be confounded due to heightened disease activity or to concomitant medications required during pregnancy. Other studies in inflammatory bowel disease and transplant populations have found no association between maternal AZA use and poor perinatal outcomes[30-33]. In experimental animals, however, 6-mercaptopurine (6-MP), an AZA metabolite, has been found to be teratogenic at doses similar to or greater than the therapeutic doses used in humans[34].

AZA and 6-MP inhibit synthesis of DNA and RNA precursors adenine and guanine, thereby exerting immunosuppressive and anti-inflammatory effects by stopping proliferation of rapidly dividing immune cells[34]. As administered, AZA is inactive, requiring non-enzymatic and enzymatic intracellular metabolism to its active metabolites, primarily 6-MP, and other inactive metabolites. 6-MP in turn is metabolized to active metabolites 6-thioguanine (6-TG) and 6-methylmercaptopurine (6-MMP). 6-TG, has been demonstrated in fetal red blood cells at slightly lower concentrations than in the red blood cells of their mothers, who were treated with AZA

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throughout their pregnancies for Crohn's disease[35]. However, the investigators in that study did not detect 6-MMP in fetal circulation, nor were any teratogenic effects noted. The authors concluded that the presence of measurable levels of one pharmacologically active thiopurine metabolite (6-TG) but not another (6-MMP) may indicate that the placenta forms a "relative barrier" to AZA and its metabolites, and recommended that a maternal level of 6-TGN (6-thioguaninenucleotides) be obtained during pregnancy in women treated with AZA to assure that the fetus is not exposed to high levels of this metabolite. However, in their series, the highest maternal 6-TGN level observed was 291pmol/8 x 10^8 RBC corresponding to 6-TGN levels in the artery and vein of the umbilical cord of 65pmol/8 x 10^8 RBC and 93 pmol/8 x 10^8 RBC, respectively, all of which are reassuringly lower than current recommended therapeutic levels for AZA treatment of 235-400 pmol/8 x 10^8 RBCs[36][37].

The possibility that thiopurine metabolites exert adverse effects on the developing fetus cannot be excluded. AZA has not been definitively linked to birth anomalies or other complications of pregnancy, and understanding of the intrauterine effects of AZA and its metabolites is clearly incomplete. Therefore our findings of significantly higher rates of SE utilization in children with *in utero* AZA exposure compared to those without exposure must be interpreted in the context of this uncertainty. It is possible that AZA metabolites may have some effect on fetal nervous system development, manifesting in early childhood as impairment in speech or hearing, or delayed learning. Alternatively, AZA may act as a marker of disease-related phenomenon.

After controlling for several potential confounders, the association of AZA exposure and SE requirement in offspring remained significant. While we cannot exclude the possibility of confounding by indication, we attempted to account for underlying disease severity by utilizing propensity scoring, and results from our models adjusting for propensity score support an independent association between AZA exposure and SE requirement in these children.

Several methodologic considerations in our study are noteworthy. First, the retrospective nature of the data acquisition regarding childhood SE requirement and developmental delays may have resulted in recall bias. However, because all of the mothers in this study had chronic disease and were unaware of specific hypotheses under investigation, we do not expect recall bias to have been different based on exposure to a specific therapeutic agent. While a number of maternal and fetal characteristics were examined in univariate fashion, we did not formally adjust for multiple comparisons, as this was a pilot study intended to inform the design of a

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larger, prospective study. It will be important to replicate the results related to AZA exposure in an independent population. Our small sample size limited the ability to account for correlations between offspring from the same mother, therefore separate models which randomly selected for one child from each mother were constructed, albeit further reducing the sample size. A larger sample size would be necessary to investigate critical windows of susceptibility to AZA exposure during gestation that may be relevant to long-term developmental outcomes. There was also a large degree of overlap among different categorizations of delays, *i.e.*, many children with a delay or special need in their first two years of life also had ADD or an educational need later on, and were included in both categories. Therefore, significance across multiple categorizations for a given characteristic is expected. Another limitation was the inability to perform formal standardized testing in the full study cohort using validated instruments, which would more fully characterize the developmental spectrum and result in less susceptibility to referral biases that may exist for reasons such as provider practice or geographic location. For example, preliminary data from the UK indicated only 2 cases of learning difficulties among 132 offspring of SLE mothers[38], in contrast to the larger proportion in our study (15 of 60 children) requiring SE services for learning or developmental delays. Prospective studies with standardized testing would enable comparisons between study populations such as children born in the UK vs US. Finally, due to the non-randomized nature of this study, it is not feasible to completely exclude the possibility that disease characteristics or severity may underlie the observed association between maternal AZA use and SE requirement in offspring, despite our attempts to account for the possibility of confounding by indication. For example, we were unable to assess longitudinal patterns of disease activity measures during the course of pregnancy, and use of propensity scoring is an imperfect way to disentangle the effects of underlying disease and its treatment.

Strengths of this study include access to a well characterized cohort of patients who were motivated and interested in participating in research. As all patients were followed at the University of Michigan, laboratory assays were standardized. The multidisciplinary research team included rheumatologists and a high risk obstetrician who brought in-depth knowledge of complicated pregnancies and perinatal risks to the review of each case. In addition, the proxy variable for developmental delays – maternal report of SE utilization – represented a clinically relevant endpoint which was apparent to a provider, and prompted intervention.

The association detected in this pilot study between SE needs and *in utero* exposure to AZA warrants further prospective study of developmental delays. We wish to emphasize that immunosuppressive therapy should not be withheld in lupus pregnancies when indicated for treatment of active disease, as highly active lupus during pregnancy is associated with poor fetal outcomes, including increase in premature birth rates and decrease in live births[39 40]. Our findings should alert pediatric providers to consider the need for early developmental screening of children born to mothers with SLE. Early identification of developmental delays, even during infancy, has been shown to increase long term functioning of affected children with appropriate intervention and treatment[41-43]. With increasing numbers of women with lupus achieving successful pregnancies, increased vigilance and understanding of long term outcomes among their children will be important for patients and providers alike.

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TABLES

Table 1. Maternal characteristics and SLE features (n=38 SLE patients)

Characteristic	No. (%) or median (IQR)
Race	
African American	5 (13)
White	25 (66)
Asian	3 (8)
Other	5 (13)
Marital status	
Married	32 (84)
Single/Div/Sep	6 (16)
Maternal age at interview (years)	36.8 (32.2, 42.2)
Maternal age at delivery (years)*	30.8 (27.8, 33.8)
Maternal education (years)	16 (16, 18)
Country of birth	
United States	34 (89)
Other	4 (11)
Number of pregnancies	2 (2, 3)
Number of children	2 (1, 2)
SLE features (ACR criteria)	
Malar rash	24 (63)
Discoid rash	3 (8)
Photosensitivity	24 (63)
Oral ulcers	18 (47)
Arthritis	36 (95)
Serositis	15 (39)
Renal Disorder	17 (45)
Neurological disorder	11 (29)
Hematological disorder	23 (61)
Immunological disorder	31 (82)
Antinuclear antibody (ANA)	34 (89)

*unit of analysis is the delivery (n=60), since some women had more than one child included in this study

Table 2. Reported developmental delays or special educational utilization, stratified by age of occurrence, among 60 children of mothers with SLE. Data expressed as frequency (percent).

Delay or special educational needs	Total (n=60)	AZA yes (n=13)	AZA no (n=47)
Age < 2 yrs	**10 (17)**	**5 (39)**	**5 (11)**
Hearing impairment	1 (2)	1 (8)	0 (0)
Fine motor skill deficit	2 (3)	1 (8)	1 (2)
Gross motor skill deficit	1 (2)	1 (8)	0 (0)
Speech delay	3 (5)	1 (8)	2 (4)
Other	4 (7)	2 (15)	2 (4)
Age ≥ 2 yrs	**14 (23)**	**7 (54)**	**7 (15)**
Aid with reading	3 (5)	0 (0)	3 (6)
Occupational therapy	2 (3)	1 (8)	1 (2)
Speech therapy	11 (18)	6 (47)	5 (11)
Attention deficit disorder	3 (5)	2 (15)	1 (2)

* 4 children had more than 1 delay

Table 3. Maternal/fetal characteristics and developmental delays/special educational needs among 60 children of mothers with SLE. Data expressed as frequency (percent) or median (interquartile range).

	No delay	Developmental Delay/SE utilization		
		Any age	Age <2 yrs	Age ≥ 2 yrs
	(n=45)	(n=15)	(n=10)	(n=14)
SLE clinical features				
SLE duration (years)	9 (5, 12)	7 (2, 9)	8.5 (3, 10)	7.5 (2, 9)
Antiphospholipid Ab Syndrome	4 (9)	5 (33)*	3 (30)	5 (36)**
Lupus nephritis (renal biopsy WHO grade ≥ III) [†]	12 (27)	7 (47)	4 (40)	6 (43)
SLE flare during pregnancy [†]	7 (16)	4 (27)	2 (20)	3 (21)
Maternal hypertension	3 (7)	3 (20)	2 (20)	3 (21)
Propensity score	0.14 (0.09, 0.22)	0.23 (0.09, 0.56)**	0.23 (0.09, 0.49)	0.28 (0.14, 0.56)***
Medications during pregnancy [§]				
Steroids, non-fluorinated				
None (0 mg)	21 (47)	5 (33)*	5 (50)	4 (29)**
Low dose (1-15 mg)	23 (51)	6 (40)*	3 (30)	6 (43)**
High dose (> 20mg)	1 (2)	4 (27)*	2 (20)	4 (29)**
Steroids, fluorinated [‡]	1 (2)	1 (7)	1 (10)	1 (7)
"Significant steroids" (High dose or fluorinated)	2 (4)	5 (33)***	3 (30)*	5 (36)***
Azathioprine	6 (13)	7 (47)**	5(50)**	7 (50)***
Mycophenolate mofetil	2 (4)	0 (0)	0 (0)	0 (0)
Hydroxychloroquine	23 (51)	7 (47)	5 (50)	6 (43)
NSAIDs	1 (2)	0 (0)	0 (0)	0 (0)
Anti-hypertensives	5 (11)	5 (33)	1 (10)	5 (36)
Perinatal characteristics				
Preeclampsia	8 (18)	5 (33)	2 (20)	5 (36)
Pregnancy duration				
<32 weeks	3 (7)	3 (20)	2 (20)	2 (14)
32-36 weeks	12 (27)	5 (33)	3 (30)	5 (36)
≥ 37 weeks	30 (67)	7 (47)	5 (50)	7 (50)
Birth weight (kg) <2.5 kg	15 (33)	8 (53)	5 (50)	7 (50)
Small for gestational age	11 (24)	4 (27)	2 (20)	4 (29)
Sex of child (female)	18 (40)	5 (33)	3 (30)	5 (36)

* p<0.10; ** p<0.05; *** p<0.01 (P-values correspond to comparison against the "no delay" group)

[†] variable included in propensity score

[§] no patients were taking methotrexate or cyclophosphamide

[‡] fluorinated steroids (*e.g.*, betamethasone, dexamethasone) administered for high risk of preterm labor

**mycophenolate mofetil contraindicated during pregnancy

Table 4. Association between AZA use and special educational service utilization among children of SLE mothers. Results from multivariable logistic regression models*

	Model A without propensity score		Model B with propensity score**	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Any age	6.12 (1.3, 30.0)	0.025	4.4 (0.8, 25.3)	0.097
Age < 2 yrs	6.18 (1.1, 36.4)	0.044	6.6 (0.9, 48.7)	0.065
Age ≥ 2 yrs	10.0 (1.8, 56.3)	0.009	6.6 (1.0, 43.3)	0.048

*All models adjust for maternal education level, duration of pregnancy, small for gestational age, and antiphospholipid syndrome.

**Propensity score includes: lupus nephritis, SLE flare during pregnancy, and non-fluorinated corticosteroid use (dose in mg)

FIGURES

Figure 1. Frequency of developmental delays in offspring of SLE mothers, by _in utero_ AZA exposure
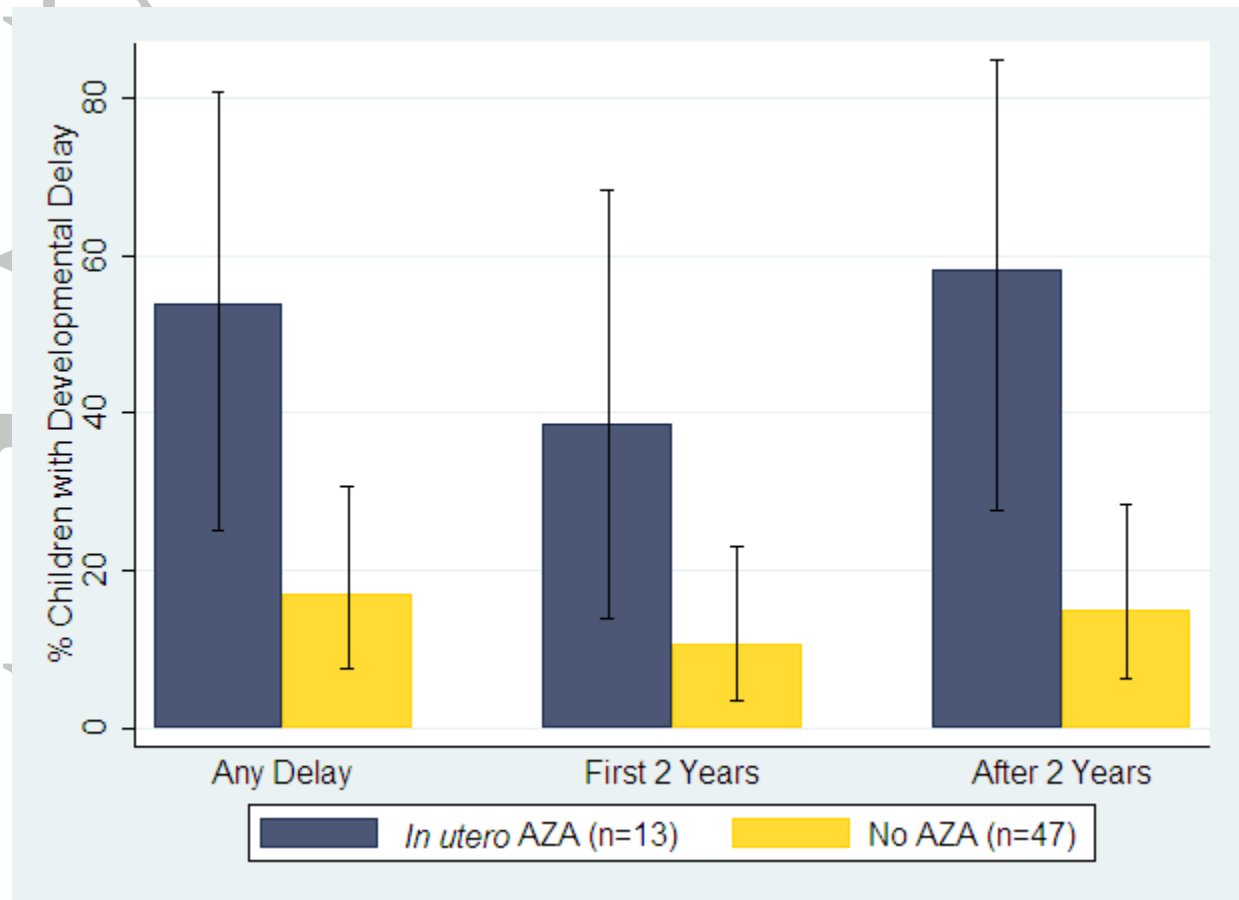
Error bars represent Clopper-Pearson exact 95% confidence intervals

"Any delay" represents delay occurring either within first 2 years of age or 2 years onward