

Original article

Outcomes of children born to mothers with systemic lupus erythematosus exposed to hydroxychloroquine or azathioprine

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Abstract

Objectives. HCQ and AZA are used to control disease activity and reduce risk of flare during pregnancy in patients with SLE. The aim of this study was to determine the outcomes of children born to mothers with SLE exposed to HCQ or AZA during pregnancy and breast-feeding.

Methods. Women attending UK specialist lupus clinics with children ≤ 17 years old, born after SLE diagnosis, were recruited to this retrospective study. Data were collected using questionnaires and from clinical record review. Factors associated with the outcomes of low birth weight and childhood infection were determined using multivariable mixed-effects logistic regression models.

Results. We analysed 284 live births of 199 mothers from 10 UK centres. The first pregnancies of 73.9% of mothers (147/199) were captured in the study; (60.4%) (150/248) and 31.1% (87/280) children were exposed to HCQ and AZA, respectively. There were no significant differences in the frequency of congenital malformations or intrauterine growth restriction between children exposed or not to HCQ or AZA. AZA use was increased in women with a history of hypertension or renal disease. Although AZA was associated with low birth weight in univariate models, there was no significant association in multivariable models. In adjusted models, exposure to AZA was associated with increased reports of childhood infection requiring hospital management [odds ratio 2.283 (1.003, 5.198), $P = 0.049$].

Conclusions. There were no significant negative outcomes in children exposed to HCQ in pregnancy. AZA use was associated with increased reporting of childhood infection, which warrants further study.

Key words: HCQ, AZA, SLE, pregnancy, adverse outcomes

Rheumatology key messages

- Hydroxychloroquine exposure in pregnancy and breastfeeding is not associated with any adverse outcomes.
- Low birth weight is associated with pre-eclampsia but not azathioprine or hydroxychloroquine use.
- Children born to mothers requiring azathioprine in pregnancy or breastfeeding need careful follow-up.

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Introduction

Immunosuppressive agents are commonly used in SLE during pregnancy, to ensure the optimum outcome for both mother and child. It is essential to ensure optimal disease control prior to and during pregnancy, as active SLE has been demonstrated to be associated with adverse maternal and foetal outcomes, including fewer live births, earlier deliveries, and small-for-gestational-age babies [1, 2]. Continuing effective medication is also important because of the increased risk of lupus flare during pregnancy or in the early post-partum period [3].

HCQ is an important drug in the management of SLE and reduces the risk of lupus flare. Women with SLE who continue HCQ throughout pregnancy have lower disease activity and lower prednisolone doses at the end of pregnancy than those who stop [4, 5]. In anti-Ro/SSA antibody-positive mothers with history of a child with congenital heart block (CHB), HCQ reduces the risk of subsequent CHB by over 50% [6]. In systematic reviews, HCQ is not associated with any increased risk of prematurity, spontaneous abortion or foetal death [7] or retinal toxicity, although early electroretinogram changes, of uncertain significance, have been reported in very small numbers of children [8].

AZA, the pro-drug of 6-mercaptopurine (6-MP), is used to treat several conditions, including SLE. AZA use (at <2 mg/kg body weight) is considered compatible with pregnancy [9], and switching from MMF to AZA prior to pregnancy is not associated with a risk of renal flare [10].

Although HCQ, AZA and glucocorticoids are considered to be compatible with pregnancy and breastfeeding [9], there are little data regarding the longer-term outcomes of children exposed to HCQ and AZA [11, 12]. The aim of this study was to determine outcomes in children up to the age of 17 exposed to HCQ or AZA *in utero* or during breastfeeding by mothers with SLE.

Methods

Participants were recruited from 10 hospital sites within the UK [Birmingham (3 sites), London (2 sites), Bath, Manchester, Blackburn, Sheffield and Southampton]. Women who had ≥ 4 1997 Updated ACR Classification Criteria for SLE [13] prior to pregnancy and who regularly attended a rheumatology outpatient department were identified.

Retrospective data were collected using a previously piloted questionnaire, between 2007 and 2011 (see [Supplementary Data S1–2](#), available at *Rheumatology* online). The first part of the questionnaire was completed by women and by collection of maternal data via interview and reviewing the medical records. Maternal data collected included: ACR Classification Criteria for SLE, lupus-related autoantibodies, and renal biopsy results. A history of APS was defined as per the 1999 preliminary Sapporo criteria [14], although did not differentiate between thrombotic and obstetric APS. Pregnancy data collected included drug exposure at conception, during pregnancy, and during breastfeeding, and the outcome in

terms of miscarriages, stillbirth, live birth, pre-eclampsia, premature delivery, intrauterine growth restriction (IUGR), birth weight and gestational age.

A second part of the questionnaire was completed by the mother to collect data on outcomes in each child up to the age of 17, including neonatal lupus rash, CHB, any other congenital malformations (using the EUROCAT definition) [15], any admissions to hospital and the diagnosis, including infections, outpatient visits and the reasons for the visits, and any evidence for developmental problems, including developmental delay (DD), special educational needs and attention deficit disorder (ADD). Due to regional variations in management of childhood infections, those requiring hospital management (either as an inpatient, outpatient or day case) were combined for analysis.

The a priori hypothesis was that exposure to HCQ or AZA during pregnancy or breastfeeding was not associated with an increased risk of congenital abnormalities, serious childhood infection, or developmental abnormalities.

The study was approved and conducted in compliance with regulations of relevant ethics committees [North West Research Ethics Committee (07/MRE08/54) and hospital research and development departments], and all mothers provided written informed consent in accordance with the Declaration of Helsinki. If a child was over the age of 12 at recruitment, then assent was given by a parent, as approved by the ethics committee.

Statistical analysis

For descriptive analyses, frequencies were compared using non-parametric tests (Mann–Whitney *U* test or χ^2 test as appropriate). Only live-born children were included. As HCQ or AZA were continued throughout pregnancy and breastfeeding in almost all cases, exposure was combined into a single variable for each drug.

As some mothers contributed more than one child to the study, univariate mixed-effects logistic regression models, with a random intercept for the mother, were used. In multivariable models, variables identified in univariate analyses and those considered to be likely confounding variables were used. Prednisolone use (yes/no) was forcibly retained in the multivariable models.

It was assumed that data regarding maternal history of LN requiring renal biopsy and hypertension were missing at random. Therefore, multiple imputation using chained equations (MICE) was conducted for these variables with 10 imputations: hypertension, renal disease, AZA use, and white ethnicity were used for MICE in the infection model, and hypertension, renal disease, AZA use, IUGR, pre-eclampsia for the low-birth-weight model. Imputed data were then used in the multivariable mixed-effects logistic regression models described above. All analyses were conducted using STATA v.16.0 (StatCorp LLC).

Results

Data were analysed for 199 women with 283 pregnancies and 284 live born children (one twin pregnancy) with

delivery dates between 1991 and 2011. Ten centres contributed data (3–134 children per centre). There was a small amount of missing data, although this was <10% for the majority of variables. The study captured 1–4 pregnancies per patient, of which 147 (73.9%) were first-ever pregnancies. The majority of patients (127/199, 63.8%) were white, 29 (14.6%) were of South Asian background and 22 (11.1%) were of Black African or Caribbean background. Hypertension predating pregnancy was present in 27/192 (14.1%) of mothers, and 42/175 (24.0%) had a previous renal biopsy; 20/199 (11.1%) of mothers had concomitant APS. The median [interquartile range (IQR)] disease duration at the time of pregnancy was 6 (3, 10) years. The demographic data of the mothers and their pregnancies are shown in Table 1, and the ACR criteria of the mothers are shown in Supplementary Table S1, available at *Rheumatology* online.

Maternal exposure to medications (HCQ and AZA)

Prednisolone and HCQ were commonly prescribed during pregnancy (167/283, 59.1% and 149/283, 52.7%, respectively). AZA was used in 86/283 (30.4%) pregnancies. In 38/283 pregnancies, all 3 medications were prescribed. In the majority of pregnancies (199/282, 70.8%), aspirin was prescribed, and aspirin use was more common in mothers also taking AZA or prednisolone (Table 2). Although the dose of aspirin was not collected, common practice at the time of the study was to use 75 mg daily. Low-molecular-weight heparin (LMWH) was used in 68/280 (24.0%) of pregnancies, of which 17 (27.9%) were in mothers with pre-existing APS. In mothers without pre-existing APS who were treated with LMWH, 17/51 (33.3%) mothers did not have a positive ACL antibody or LA.

There were no significant differences in the characteristics of mothers who received HCQ compared with those who did not. However, mothers receiving AZA were more likely to have a history of hypertension (31.1% vs 6.6%, $P < 0.001$) or a renal biopsy prior to pregnancy (52.1% vs 13.4% $P = 0.007$), proteinuria (32.4% vs 18.5%, $P = 0.014$), a longer duration of disease [median (IQR)] [7.5 (5, 11) vs 5 (2, 10) years, $P = 0.003$], a previous positive anti-RNP antibody (39.3% vs 20.4%, $P = 0.007$) and to be taking aspirin during the pregnancy (81.2% vs 66.3%, $P = 0.012$) (see Table 2). Of the 66 patients with proteinuria, 16 (24.2%) had pre-eclampsia.

Pregnancy outcomes and exposure to HCQ or AZA

Of 284 children (from 283 pregnancies), 149/284 (52.5%) were exposed to HCQ and 87/284 (30.6%) were exposed to AZA. The median gestational age was 38 (37, 39) weeks. Of 103/279 (36.9%) of births <38 weeks, 12/99 (12.1%) were induced due to pre-eclampsia and 15/94 (16.0%) were induced due to IUGR. In induced pregnancies, the median gestational age was 36 (32, 38) weeks. The median birth weight was 2.96 (2.49, 3.31) kg and 70/276 (25.4%) babies were <2.5 kg. Of the babies

TABLE 1 Characteristics of the mothers and their pregnancies in the cohort

Mothers in the cohort (n = 199)	
Age at delivery of first child in study (years) (n = 194)	31 (28, 35)
Ethnic background	
African or Caribbean	22 (11.1%)
South Asian	29 (14.6%)
White	127 (63.8%)
Chinese	4 (2.0%)
Other/Mixed	11 (5.5%)
Unknown	6 (3.0%)
Number of pregnancies per patient captured in this study	
1	127 (63.8%)
2	60 (30.2%)
3	11 (5.53%)
4	1 (0.5%)
Number of first pregnancies in this study	147 (73.9%)
Anti-dsDNA ever present (n = 191)	121 (63.4%)
Anti-Sm ever present	27 (14.4%)
Anti-RNP ever present	49 (25.7%)
Previous renal biopsy (n = 175)	42 (24.0%)
Hypertension prior to pregnancy (n = 192)	27 (14.1%)
Diagnosis of APS (n = 181)	20 (11.1%)
Pregnancies (n = 283)^a	
Disease duration at time of pregnancy (years)	6 (3, 10)
Autoantibodies	
Anti-Ro/SSA (n = 263)	108 (41.1%)
Anti-La/SSB (n = 261)	55 (21.1%)
Anti-Ro/SSA or anti-La/SSB (n = 261)	111 (42.5%)
APS serology	
aCL (n = 250)	67 (26.8%)
LA (n = 258)	92 (35.8%)
Positive LA or aCL (n = 248)	121 (48.8%)
Proteinuria during pregnancy (n = 250)	67 (36.6%)
Medication use during pregnancy (n = 283)	
Prednisolone exposure during pregnancy	167 (59.1%)
HCQ exposure during pregnancy	149 (52.7%)
AZA exposure during pregnancy	86 (30.4%)
Prednisolone + HCQ	58 (20.5%)
Prednisolone + AZA	0
HCQ + AZA	43 (15.2%)
Prednisolone + HCQ + AZA	38 (13.4%)
Prednisolone alone	34 (12.0%)
Aspirin (n = 282)	199 (70.8%)
Low-molecular-weight heparin (n = 280)	68 (24.0%)

^a283 pregnancies with 284 live births due to 1 set of twins.

with low birth weight, 22/70 (31.4%) were reported to have IUGR.

Congenital abnormality (as defined by EUROCAT CA) occurred in 6 (2.1%) pregnancies. All 6 cases of neonatal lupus rash occurred in pregnancies with concomitant positive anti-Ro/SSA and/or La/SSB antibodies [rate of 6/111 (5.4%) in Ro/SSA/La/SSB-positive mothers, 6/284 (2.1%) overall]. Of the 7 children with CHB [overall 7/284 (2.46%)], one was born to a mother without positive anti-Ro/SSA or La/SSB antibodies. Of these 7 children, 4 had been exposed to HCQ and 3 not (including the 1 child whose mother did not have Ro/SSA/La antibodies).

TABLE 2 Characteristics of mothers and their pregnancies according to exposure to AZA or HCQ

Mothers (n = 199)										
	All mothers	HCQ			AZA			Prednisolone		
		Exposed (n = 107)	Not exposed (n = 92)	P	Exposed (n = 59)	Not exposed (n = 140)	P	Exposed (n = 118)	Not exposed (n = 81)	P
Ethnic background (White)	127 (63.8%)	73 (68.2%)	54 (58.7%)	0.163	36 (61.0%)	91 (65.0%)	0.593	71/118 (60.2%)	56/81 (69.1%)	0.916
Anti-dsDNA ever	121/187 (64.7%)	63/97 (64.6%)	58/90 (64.4%)	0.943	41/55 (74.6%)	80/132 (60.6%)	0.069	79/110 (71.8%)	42/77 (54.6%)	0.015
Anti-Smith ever	27/184 (14.7%)	13/97 (13.4%)	14/87 (16.1%)	0.607	9/55 (16.4%)	18/129 (4.0%)	0.672	21/112 (18.8%)	6/72 (8.3%)	0.051
Anti-RNP ever	49/188 (26.1%)	24/100 (24.0%)	25/88 (28.4%)	0.492	22/56 (39.3%)	27/20 (20.4%)	0.007	35/113 (31.0%)	14/74 (18.7%)	0.600
Previous renal biopsy	42/175 (24.0%)	21/99 (21.1%)	21/76 (27.6%)	0.324	25/48 (52.1%)	17/127 (13.4%)	<0.001	32/102 (21.4%)	10/73 (13.7%)	0.007
Hypertension prior to pregnancy	27/192 (14.1%)	10/103 (9.7%)	17/89 (19.1%)	0.062	18/56 (32.1%)	9/136 (6.6%)	<0.001	22/113 (19.5%)	5/79 (6.3%)	0.010
Diagnosis of APS	20/181 (11.1%)	10 (10.1%)	10/82 (12.2%)	0.655	4/53 (7.6%)	16/128 (12.5%)	0.333	12/106 (11.3%)	8/75 (10.7%)	0.890

Pregnancies (n = 283)										
	All pregnancies	HCQ			AZA			Prednisolone		
		Exposed (n = 150)	Not exposed (n = 134)	P	Exposed (n = 86)	Not exposed (n = 198)	P	Exposed (n = 167)	Not exposed (n = 116)	P
Age at delivery (years)	32 (28, 35)	32 (29, 35)	31 (28, 35)	0.172	32 (29, 35)	32 (28, 35)	0.544	32 (29, 35)	32 (28, 35)	0.445
Disease duration (years)	6 (3, 10)	6 (3, 10)	7 (3, 11)	0.126	7.5 (5, 11)	5 (2, 10)	0.003	6 (3, 10)	5.5 (3, 10)	0.325
Anti-Ro/SSA	108/262 (41.1%)	53/141 (37.6%)	55/121 (45.5%)	0.197	36/77 (46.8%)	72/185 (38.9%)	0.241	68/153 (44.4%)	40/109 (36.7%)	0.209
Anti-La/SSB	55/260 (21.2%)	23/139 (16.6%)	32/121 (26.5%)	0.051	22/77 (28.6%)	33/183 (18.0%)	0.057	36/153 (23.5%)	19/107 (17.8%)	0.262
Anti-Ro/SSA or anti-La/SSB	111/260 (42.7%)	54/139 (38.9%)	57/121 (47.1%)	0.179	37/77 (48.1%)	74/183 (40.4%)	0.243	70/153 (45.8%)	41/107 (38.3%)	0.233
aCL	67/249 (26.8%)	33/131 (25.2%)	34/118 (28.8%)	0.520	25/72 (34.7%)	42/177 (23.7%)	0.076	40/144 (27.8%)	27/105 (25.7%)	0.717
LA	92/257 (35.8%)	52/136 (38.2%)	40/121 (33.1%)	0.387	30/73 (41.1%)	62/184 (33.7%)	0.264	58/149 (38.9%)	34/108 (31.5%)	0.219
Aspirin	199/281 (70.8%)	111/149 (74.5%)	88/132 (66.7%)	0.150	69/85 (81.2%)	130/196 (66.3%)	0.012	133/165 (80.6%)	66/116 (59.9%)	<0.001
LMWH	68/280 (24.6%)	41/148 (27.7%)	27/132 (20.4%)	0.158	27/85 (31.8%)	41/195 (21.0%)	0.054	45/165 (27.2%)	23/115 (20.0%)	0.163
Proteinuria	66/248 (26.8%)	35/132 (25.8%)	32/116 (27.6%)	0.745	26/75 (34.7%)	40/173 (23.1%)	0.059	47/145 (32.4%)	19/103 (18.5%)	0.014

Comparisons made using Chi² tests or Mann–Whitney U tests as appropriate. Each drug was considered independently. Bold text indicates statistically significant results. LMWH: low-molecular-weight heparin. P < 0.05 was considered statistically significant.

The median follow-up of children was 3.23 (1.14, 6.88) years. The follow-up duration was shorter in children exposed to HCQ [2.21 (0.58, 4.74) vs 4.55 (2.04, 9.34) years, $P < 0.001$], but there was no difference between children exposed or not to AZA. There were 99 infections requiring hospital management (either as an inpatient or outpatient) in 48/284 (16.9%) children. Among children with reported infection, the median (IQR) number of infections was 2 (1, 3). 17/284 (6.0%) had one or more of DD, ADD, special needs or a requirement for special schooling. Reported infections are described in more detail below.

There were significant differences between outcomes in pregnancies in which AZA was used and those in which it was not (Table 2). Children exposed to AZA were delivered at an earlier gestational age [37 (35, 38) vs 38 (37, 40) weeks, $P < 0.001$] and were more likely to be premature (<38 weeks gestation) [44/86 (51.2%) vs 59/193 (30.6%), $P = 0.001$]. Similarly, babies were more likely to be smaller in birth weight. There was also a greater number of children with childhood infection in those exposed to AZA [21/87 (24.1%) vs 27/197 (13.7%), $P = 0.031$]. There were no differences in the reported frequency of pre-eclampsia, IUGR (or induction for either of pre-eclampsia or IUGR), CHB or other congenital abnormality (Table 3). Fewer children were reported to have special needs in the group exposed to HCQ [1/148 (0.7%) vs 6/135 (4.4%), $P = 0.041$], but this was not significant when combined with DD and ADD [6/149 (4.0%) vs 11/135 (8.2%), $P = 0.144$].

Maternal and pregnancy factors associated with low birth weight

As low birth weight (<2.5 kg) was more common in children exposed to AZA, a two-level mixed-effects logistic regression model, with the mother as the random intercept, was used. In univariate analyses, exposure to AZA, aspirin and LMWH, and pre-eclampsia were all associated with low birth weight. There was no association with APS, aCL or LA. In multivariable models using the variables above, only pre-eclampsia [OR 4.2 (1.07, 16.65), $P = 0.040$] was independently associated with low birth weight (Table 4). Given that birth weight is reported to increase with subsequent pregnancies, in a sensitivity analysis, the number of pregnancies was included in the multivariable model. In this sensitivity analysis, only pre-eclampsia [OR 5.11 (1.62, 16.19) $P = 0.005$] was associated with low birth weight, as before. These findings were also observed in a model in which maternal history of hypertension and renal biopsy were imputed (Table 4).

Maternal and pregnancy-related risk factors for childhood infection

Infections requiring hospital management were reported in 48/284 (16.9%) children during the follow-up period. To avoid bias from recurrent infections in some children, we analysed risk factors based on the first recorded

infection; the most frequent were pneumonia (10/48, 20.8%), bronchiolitis (7/48, 14.6%) and pharyngitis/tonsillitis (4/48, 8.4%) (Table 5).

In univariate analyses, both AZA use and mother being of white background were significantly associated with childhood infection. Duration of follow-up and prednisolone use was forcibly retained in the multivariable models. In both the multivariable model (including gestational age and birth weight) and the imputed model (also including maternal history of hypertension and renal disease), white background and AZA exposure remained statistically significant (Table 6). In a sensitivity analysis of first-ever pregnancies (146 women), exposure to AZA remained associated with childhood infection in both univariate [OR 3.21 (1.34, 7.66) $P = 0.009$] and multivariable models [OR 2.72 (1.67, 3.64) $P = 0.02$] using the same covariates above. In children with infection, there was no difference in the number of reported infections per child in those exposed to AZA compared with those who were not [2 (1, 2) vs 2 (1, 4), $P = 0.997$].

Discussion

This is one of the largest studies examining outcomes in children born to mothers with SLE beyond the early post-natal period. Children were included up to the age of 17 years, capturing events both in early and late childhood.

The study focused on associations between HCQ and AZA exposure during pregnancy and low birth weight and childhood infection. Other outcomes, including pre-eclampsia, IUGR, congenital malformation, neonatal lupus rash and CHB, were infrequent in our study and did not differ in frequency between groups exposed to HCQ or AZA. The rates of CHB or other congenital abnormalities in this study were 2.5% and 2.1%, respectively. The prevalence of CHB was similar to that previously reported [16], but greater than the 1/154 observed in anti-Ro/SSA-positive mothers in the PROMISSE study [17]. Our study did not include data from prior pregnancies, which may influence the risk of CHB (i.e. up to 20% if a previous child had CHB), although the first pregnancy was captured in nearly 75% of mothers. The lower rates of CHB in the PROMISSE study may also be due to increased HCQ use (64.7% compared with 52.7% in our study).

HCQ is recommended for all women with SLE during pregnancy [18, 19]; it reduces the risk of CHB [6] and may reduce the incidence of pre-eclampsia, although data are conflicting [20]. In our study, there was no increased pre-term birth, IUGR or congenital abnormality in children exposed to HCQ. Of note, the number of patients taking HCQ was relatively modest, reflecting clinical practice at the time of the study. Although there was no difference in the frequency of CHB in children exposed to HCQ, the total number of children with CHB was small. A number of studies have confirmed the safety of HCQ in pregnancy. A meta-analysis including studies up to 2014 inclusive (7 cohort studies and 1

TABLE 3 Pregnancy outcomes according to exposure to AZA or HCQ in all pregnancies/children (univariate analysis)

	All children (n = 284)	HCQ			AZA		
		Exposed (n = 149)	Not exposed (n = 135)	P	Exposed (n = 87)	Not exposed (n = 197)	P
Characteristics of children							
Age of child at time of study (years) (n = 284)	3.23 (1.14, 6.88)	2.21 (0.58, 4.74)	4.55 (2.04, 9.34)	<0.001	3.28 (1.14, 8.31)	3.11 (1.08, 6.35)	0.682
Gestational age at delivery (weeks) (n = 280)	38 (37, 39)	38 (37, 39)	38 (37, 39)	0.416	37 (35, 38)	38 (37, 40)	<0.001
Pre-term delivery at <38 weeks (n = 280)	103/279 (36.9%)	58/148 (39.2%)	45/131 (34.4%)	0.403	44/86 (51.2%)	59/193 (30.6%)	0.001
Delivery method (n = 281)							
Vaginal	139 (49.6%)	71 (49.0%)	68 (50.4%)	0.967	48 (55.8%)	91 (47.2%)	0.151
Assisted	30 (10.7%)	16 (11.0%)	14 (10.4%)		5 (5.8%)	25 (12.8%)	
Caesarean section	111 (39.5%)	58 (39.7%)	53 (39.3%)	0.915	33 (38.4%)	78 (40.0%)	0.018
Birth weight (kg) (n = 277)	2.96 (2.49, 3.31)	2.92 (2.49, 3.31)	3.00 (2.50, 3.34)		2.77 (2.32, 3.28)	3.00 (2.57, 3.34)	
Low birth weight (<2.5 kg) (n = 277)	70/276 (25.4%)	39/146 (26.7%)	31/130 (23.9%)	0.585	29/83 (34.9%)	41/193 (21.2%)	0.016
Adverse outcomes during pregnancy reported by mothers							
Pre-eclampsia	328/267 (10.5%)	15/142 (10.6%)	13/125 (10.4%)	0.982	11/82 (13.4%)	17/185 (9.2%)	0.299
Pre-eclampsia requiring induction (n = 269)	19/268 (7.1%)	13/143 (9.1%)	6/125 (4.8%)	0.172	7/82 (8.5%)	12/186 (6.5%)	0.532
IUGR (n = 268)	31/267 (11.6%)	16/140 (11.4%)	15/127 (11.8%)	0.906	10/82 (12.2%)	21/185 (11.4%)	0.843
IUGR requiring induction	19/267 (7.1%)	10/140 (7.1%)	9/127 (7.1%)	0.986	7/82 (8.5%)	12/186 (6.4%)	0.540
Induction (either PET or IUGR)	32/283 (11.3%)	19/149 (12.8%)	13/134 (9.7%)	0.419	12/86 (13.8%)	20/197 (10.2%)	0.353
Neonatal outcomes reported by mothers							
Neonatal lupus rash (all children)	6/284 (2.1%)	4/149 (2.7%)	2/135 (1.5%)	0.481	2/87 (2.3%)	4/197 (2.0%)	0.885
Congenital Heart Block (CHB)	7/284 (2.5%)	4/149 (2.7%)	3/135 (2.2%)	0.802	2/87 (2.3%)	5/197 (2.5%)	0.905
Congenital abnormality (EUROCAT CA)	6/284 (2.1%)	4/149 (2.7%)	2/135 (1.5%)	0.486	2/87 (2.3%)	4/197 (2.0%)	0.885
Infection	48/284 (16.9%)	24/149 (16.1%)	24/139 (17.8%)	0.708	21/87 (24.1%)	27/197 (13.7%)	0.031
Developmental delay, attention deficit disorder, special schooling or special needs	17/284 (6.0%)	6/149 (4.0%)	11/135 (8.2%)	0.144	6/87 (6.9%)	11/197 (5.6%)	0.667
Developmental delay	14/283 (5.0%)	6/148 (4.1%)	8/135 (5.9%)	0.679	5/87 (5.8%)	9/196 (4.6%)	0.679

(continued)

TABLE 3 Continued

	All children (n = 284)		HCQ		AZA	
	Exposed (n = 149)	Not exposed (n = 135)	Exposed (n = 87)	Not exposed (n = 197)	P	P
Attention deficit disorder	3/283 (1.1%)	3/135 (2.2%)	0	3/196 (1.5%)	0.068	0.246
Special schooling	6/283 (2.1%)	5/135 (3.7%)	1/148 (0.7%)	4/196 (2.0%)	0.077	0.0889
Special needs	7/283 (2.5%)	6/135 (4.4%)	1/148 (0.7%)	4/196 (2.0%)	0.041	0.482

Data are n (%) or median (IQR) as appropriate. Comparisons made using the Chi² test for categorical variables or the Mann–Whitney U test for continuous variables. Bold text indicates statistically significant results. IUGR: intrauterine growth restriction. P < 0.05 was considered statistically significant.

RCT) compared outcomes between 800 HCQ-exposed and 1130 control pregnancies and confirmed no increased risk of low birth weight or congenital abnormalities with HCQ exposure [21]. A subsequent large cohort study of patients with a spectrum of autoimmune diseases also supports the safety of HCQ [22]. In contrast, a population-based cohort study by Huybrechts *et al.* (2021) reported an increased risk congenital malformation babies exposed to HCQ during the first trimester [adjusted relative risk (RR) 1.26 (1.04, 1.54)]. Importantly, the mean (S.D.) daily dose of HCQ was high 371 (379) mg, and the increased risk only occurred in mothers receiving ≥400 mg/day [23]. Although the dose was not recorded in our study, the authors are not aware of any woman receiving a dose of >400 mg/day.

There was no increased risk of childhood infection or developmental problems with HCQ exposure. There was a small reduction in the number of children with special needs, but the number of children was small and the follow-up durations shorter in children exposed to HCQ; therefore, this observation should be interpreted with caution. A Danish study examined school performance in children and reported no statistically significant difference between children exposed to HCQ and/or other immunosuppressants with those who were not. In this large population-based study (including 312 children of mothers with SLE), SLE diagnosis and medication exposure were identified using ICD-10 codes and prescriptions collected during pregnancy [24]. In contrast, in our study all women fulfilled classification criteria for SLE and confirmed that they were taking the medication as prescribed. Although a smaller study of 40 patients of children born to mothers with SLE and/or APS used different outcome measures, the frequency of cognitive impairment was 7%, similar to the 6% observed using our combined measure [25].

Fewer studies have investigated the safety of AZA in pregnancy. We did not find any association between AZA use and pre-eclampsia or IUGR. Associations between AZA and low birth weight and preterm birth were only observed in univariate analyses and not in multivariable models. As might be expected, mothers receiving AZA were more likely to have a history of renal disease or hypertension and were therefore included our models. Our findings are comparable with those of previous studies, demonstrating no adverse early post-partum outcomes in patients with SLE [26] or inflammatory bowel disease (IBD) receiving AZA [27, 28]. Earlier studies in IBD suggested an increased risk of congenital abnormalities, but confounding effects of active disease or concomitant medication are likely to be important [29].

A smaller retrospective study by Marder *et al.* (2013) reported that AZA exposure was associated with increased special educational service use, especially in children over 2 years of age [30]. Our study, in which approximately one-third of children had reached school age, did not find such an association and supports findings of a smaller study in children of mothers with IBD [31] and a study of 92 children of mothers with SLE,

TABLE 4 Mixed-effects logistic regression model of low birth weight in all pregnancies ($n = 283$)

	Univariate model			Multivariable model (only variables included in the model are shown)			Imputed multivariable model ^a		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Fixed maternal factors									
Ethnic background (White)	0.886	0.387, 2.030	0.776						
History of hypertension	2.569	0.847, 7.796	0.096				1.142	0.739, 4.526	0.192
History of renal disease	1.933	0.691, 5.411	0.209				0.709	0.198, 2.544	0.593
APS ^b	1.877	0.486, 7.253	0.361						
LA	1.452	0.590, 3.569	0.417						
aCL	1.749	0.613, 4.986	0.295						
dsDNA (ever)	1.516	0.614, 3.745	0.367						
Sm (ever)	1.806	0.542, 6.023	0.336						
RNP (ever)	0.956	0.373, 2.450	0.925						
Pregnancy factors									
Maternal age at delivery	1.012	0.936, 1.091	0.785						
Maternal disease duration	0.969	0.892, 1.051	0.444						
Pregnancy number	0.870	0.609, 1.242	0.444						
Pre-eclampsia	6.315	1.882, 21.195	0.003	5.262	1.654, 16.747	0.005	5.829	1.835, 18.519	0.003
Proteinuria	1.503	0.601, 3.763	0.384						
HCQ	1.237	0.576, 2.656	0.585						
AZA	2.554	1.085, 6.012	0.032	1.749	0.715, 4.279	0.221	1.829	0.739, 4.526	0.192
Prednisolone	1.833	0.849, 3.959	0.123	1.228	0.524, 2.878	0.637	1.269	0.583, 2.759	0.548
Aspirin	2.485	1.050, 6.183	0.039	2.072	0.715, 4.279	0.160	1.666	0.702, 3.954	0.247
LMWH	2.264	1.019, 5.030	0.045	1.899	0.806, 4.475	0.143	1.845	0.833, 4.090	0.131
Ro/SSA (current)	1.240	0.532, 2.892	0.618						
La/SSB (current)	2.460	0.823, 7.358	0.107						

^aIn the imputed model, data for hypertension and renal disease were imputed using chained equations (see Methods for more details). ^bThere was no change in APS status between pregnancies. Bold text indicates statistically significant results. LMWH: low-molecular-weight heparin. $P < 0.05$ was considered statistically significant.

TABLE 5 First documented infections during childhood requiring hospital management in 284 children

Infection	Frequency (n, %)
Brain abscess	1 (2.08%)
Bronchiolitis	7 (14.58%)
CMV	1 (2.08%)
Chickenpox	1 (2.08%)
Conjunctivitis	1 (2.08%)
Ear infection	1 (2.08%)
Febrile convulsions	4 (8.33%)
Meningitis	3 (6.25%)
Unspecified bacterial infection requiring antibiotics	2 (4.16%)
Pharyngitis or tonsillitis	4 (8.33%)
Pneumonia	11 (22.9%)
Pyrexia of unknown origin (assumed infective)	1 (2.08%)
Urinary tract infection	6 (12.50%)
Unspecified viral infection	3 (6.25%)
Wound infection	2 (4.16%)

which did not identify an increased risk of neurodevelopmental disorders up to mean 14 years of age [32] There was a similar frequency of patients of white and black

backgrounds in our study to those above, although we included more patients from Asian backgrounds. There may also be differences in assessment of children by special needs services, notably hearing services, between the USA and UK.

Children with low birth weight were more likely to have been exposed to AZA *in utero*, although the frequency of babies born <2.5 kg was lower than reported by others [27]. In univariate models, low birth weight was associated with AZA, aspirin and LMWH, but this is likely due to the confounding effect of pre-eclampsia. It is therefore important to adjust for maternal variables in models of early pregnancy outcomes.

Childhood infection requiring hospital management was reported more frequently in children exposed to AZA. As both low birth weight and prematurity are associated with increased childhood infection risk, these were forcibly retained in our models [33]. Similarly, children with a longer period of follow-up may be more likely to have infection, and therefore the follow-up duration was also retained in the multivariable model. Although the foetal liver is unable to convert AZA to 6-mercaptopurine, the active metabolite 6-TGN (but not 6-MMP) is present in both the maternal and foetal circulation and is proposed to contribute to anaemia in children exposed

TABLE 6 Mixed-effects logistic regression model of infection in children from all pregnancies (*n* = 283)

	Univariate model			Multivariable model (only variables included in the model are shown)			Imputed multivariable model ^a		
	OR	95% CI	<i>P</i>	OR	95% CI	<i>P</i>	OR	95% CI	<i>P</i>
Fixed maternal factors									
Ethnic background (white)	2.445	1.107, 5.398	0.027	2.870	0.567, 2.365	0.017	2.776	1.164, 6.620	0.021
History of hypertension	1.759	0.679, 4.560	0.245				1.050	0.293, 3.761	0.940
History of renal disease	1.057	0.467, 2.397	0.898				0.770	0.240, 2.472	0.659
APS ^b	0.539	0.146, 1.992	0.355						
LA	0.944	0.452, 1.972	0.879						
aCL	1.067	0.492, 2.318	0.869						
dsDNA (ever)	1.211	0.534, 2.749	0.646						
Sm (ever)	1.351	0.475, 3.836	0.572						
RNP (ever)	0.842	0.364, 1.947	0.687						
Pregnancy factors									
Maternal age at delivery	1.047	0.979, 1.112	0.180						
Maternal disease duration	0.975	0.906, 1.049	0.501						
Pregnancy number	0.870	0.609, 1.241	0.442						
Birth weight	0.858	0.518, 1.423	0.554	1.158	0.567, 2.365	0.687	1.157	0.568, 2.360	0.688
Low birth weight (<2.5 kg)	1.721	0.815, 3.635	0.154						
Gestational age	0.919	0.812, 1.040	0.180	0.925	0.770, 1.109	0.400	0.922	0.768, 1.106	0.380
Premature delivery (<38 weeks)	1.611	0.746, 3.480	0.224						
Pre-eclampsia	0.566	0.152, 2.101	0.395						
IUGR	1.021	0.322, 3.242	0.971						
Proteinuria	0.831	0.319, 2.160	0.704						
HCCQ	0.858	0.423, 1.739	0.671						
AZA	2.221	1.027, 4.804	0.043	2.283	1.003, 5.198	0.049	2.432	1.008, 5.870	0.048
Prednisolone	1.372	0.660, 2.853	0.397	1.217	0.538, 2.753	0.637	1.218	0.539, 2.745	0.636
Aspirin	1.423	0.672, 3.011	0.357						
LMWH	1.418	0.685, 2.936	0.347						
Ro/SSA (current)	0.782	0.385, 1.594	0.500						
La/SSB (current)	1.020	0.433, 2.403	0.964						
Age of child at recruitment/ Follow-up duration (years) ^c	1.024	0.942, 1.112	0.574	1.010	0.929, 1.097	0.822	1.009	0.927, 1.098	0.836

^aIn the imputed model, data for hypertension and renal disease were imputed using chained equations (see methods for more details). ^bThere was no change in APS status between pregnancies. ^cAge of recruitment, which defines the follow-up period of the child, was forcibly retained in the model. Bold text indicates statistically significant results. IUGR: intrauterine growth restriction; LMWH: low-molecular-weight heparin; OR: odds ratio. *P* < 0.05 was considered statistically significant.

to AZA *in utero* [34]. Other studies, however, suggest that there are no significant differences in lymphocyte count or function due to AZA exposure [35, 36].

A large study of children born to women with IBD receiving AZA with a follow-up of 5 years found no increased risk of infection requiring antibiotics in 240 children [37]. Similarly, a smaller Dutch study of mothers with IBD and follow-up duration similar to our study did not identify increased frequency of severe infection or attendance at primary care in children exposed to AZA in pregnancy/breastfeeding [31]. Our observation may relate to other important unmeasured confounders or increased risk of recall bias over the longer follow-up duration, especially in mothers taking immunosuppressants. Additional unmeasured confounders, including socio-economic factors, may also be important.

It was not possible to study only infections that occurred during breastfeeding although only very low

concentrations of 6-MP, and no AZA metabolites, are detected in breast milk [38–40]. In this study, the mother being of a white ethnic group was associated with childhood infection. This could reflect increased childcare usage by this group, which may increase exposure to infection [41]. Alternatively, our study only considered infection requiring secondary care intervention, and fewer outpatient appointment attendances by children from black backgrounds compared with white backgrounds have been reported [42]. Furthermore the number of mothers from non-white backgrounds was small, consistent with known challenges in recruiting women from these backgrounds into research studies.

Strengths of the study

This is the one of the largest studies of outcomes in children born to mothers with SLE extending beyond the

early postnatal period. As women provided data about multiple children, random-effects logistic regression models were used to allow inferences to be made about the exposures and outcome that were not dependent on unmeasured variables related to the mother.

Limitations of the study

Data completed by the mothers are at risk of recall bias, which may be higher in those who continued medication throughout pregnancy. Our study focused on live-born children and is therefore not able to detect any effects of either SLE itself or medication on late pregnancy losses (these events were excluded as there were concerns about the completeness of the data, as some women declined to take part in the study). Information on drug dose was not available precluding examination of dose-dependent relationships. Similarly, changes in drug dosage during pregnancy were not captured. Women receiving AZA were more likely to have a history of renal disease or hypertension, suggesting more severe SLE. Although these factors were adjusted for in the models, there may be therefore other unmeasured confounders related to either the mother or the child contributing to the association between AZA and pregnancy outcomes in this study.

In summary, this large retrospective observational study of pregnancy outcomes in patients with SLE has confirmed that adverse events are relatively rare. HCQ remains a treatment compatible with pregnancy and breastfeeding. AZA was not associated with adverse events in either the mother or foetus. Children who were exposed to AZA during pregnancy/breastfeeding appeared to have a slightly increased risk of infection, but the underlying mechanism is uncertain. We support the view of others [43] that larger prospective pregnancy studies, with lupus patients from diverse racial, ethnic and socio-economic backgrounds, a core minimum dataset and frequent follow-up are required to provide more definitive data that will exclude recall bias and reduce the risk of unmeasured confounders.

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Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author, dependent upon the nature of the request, the availability of the data and its intended use.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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