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Risk of infantile hemangiomas in the offspring of women with autoimmune disease and the pathogenic implications of these lesions

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Abstract

The purpose of this study was to analyze the risk of maternal autoimmune disease or associated treatments on infantile hemangiomas (IHs), a common benign vascular tumor in infants, and to better understand how maternal chronic inflammation may play a factor in the pathogenesis of these lesions. Eligible women from the United States and Canada who enrolled before 19 weeks' gestation and delivered at least one live born infant were recruited as part of the Organization of Teratology Information Specialists (OTIS) Autoimmune Disease in Pregnancy Project from 2004–2013. A total of 51/969 (5.3%) and 8/240 (3.3%) infants with IH were born to mothers with and without autoimmune disease, respectively (OR 1.61; 95%CI, 0.75–.44). The presence of ulcerative colitis (UC) in the mother was significantly associated with IH in the child (OR 3.46; 95%CI, 1.29–9.26). The five largest IH occurred within the autoimmune disease cohort and to women taking a biologic medication. These results imply that UC may be a risk factor for IH development, and that chronic inflammation may influence the development of these lesions. This potential link between IH and autoimmune disease warrants further investigation.

Keywords

autoimmune; biologics; birth defects; infantile hemangioma; pregnancy

1 | INTRODUCTION

Infantile Hemangiomas (IHs) are the most common tumor of infants, characterized by appearance in early infancy and ultimate regression with time. They are benign tumors that are estimated to occur in approximately 4–5% of the general population (Kilcline & Frieden, 2008; Munden et al., 2014). The severity of IHs varies widely, and lesions that are larger or

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CONFLICTS OF INTEREST

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have the potential to cause complications and/or interfere with vital structures may require aggressive treatment. While the pathogenesis of IHs is not well understood, many theories involving tissue hypoxia and hypoxia-related growth factors have been suggested, as well as more recent evidence that embolization of placental chorionic villous mesenchymal core cells (PCVMCCs) might play a role (de Jong, Itinteang, Withers, Davis, & Tan, 2016; Itinteang, Vishvanath, Day, & Tan, 2011).

A connection may exist between IHs and autoimmune disease. Known risk factors for IH development include low birth weight (LBW), female sex, preterm delivery, multiple gestation pregnancies, as well as amniocentesis, and chorionic villous sampling in the mother (Alfirevic, Sundberg, & Brigham, 2003; Bauland, Smit, Bartelink, Zondervan, & Spauwen, 2010; Burton, Schulz, Angle, & Burd, 1995; Haggstrom et al., 2007). Many of these same perinatal complications, particularly preterm delivery and LBW, are also observed more frequently in pregnant women with autoimmune conditions such as inflammatory bowel disease (IBD) and rheumatoid arthritis (RA) (Abdul Sultan et al., 2016; Langen, Chakravarty, Liaquat, El-Sayed, & Druzin, 2014; Lin, Chen, Lin, & Chen, 2010; Shand, Chen, Selby, Solomon, & Roberts, 2016). Furthermore, many of the same hypoxia-related cytokines and growth factors associated with IH development have been implicated in the disease pathogenesis of these chronic inflammatory conditions (Gaber, Dziurla, Tripmacher, Burmester, & Buttgereit, 2005; Konisti, Kiriakidis, & Paleolog, 2012; Scaldaferri et al., 2009; Xu & Dong, 2016).

This study was undertaken to analyze the risk of maternal autoimmune disease and associated treatments on IHs to provide more insight into the role of maternal inflammation in IH pathogenesis. To our knowledge, this is the first study to examine the potential association between the presence of autoimmune disease and this particular fetal outcome.

2 | MATERIALS AND METHODS

2.1 | Source of the sample

Data for this analysis were obtained from the Organization of Teratology Information Specialists (OTIS) Autoimmune Disease in Pregnancy Project, a prospective cohort study of pregnancy outcomes among women in the United States and Canada. Participants in the study were recruited from pregnant callers to OTIS counseling services throughout the United States and Canada who initiated contact with an OTIS service with questions about any exposure in pregnancy, as well as direct marketing to consumers through social media and the OTIS Mother-ToBaby study website. Participants were also recruited through direct marketing to rheumatologists, gastroenterologists, dermatologists, neurologists, obstetricians, nurses, and other health care professionals through mail, professional meetings, and the website. Women were eligible for the overall cohort study if they enrolled prior to 19 completed weeks' gestation, and had not enrolled in this study with a previous pregnancy. Pregnant women who enrolled in the study between 2004 and 2013, and delivered at least one live born infant were eligible for the analysis. To increase the reliability and validity of the diagnosis of IH, the sample was further restricted to the subset of infants that received a blinded physical examination by a study dysmorphologist for the presence or absence of major and minor physical features including IH. The protocol was

approved by the institutional review board at the University of California, San Diego. All women in the study initially provided oral consent for participation, and subsequently provided written consent for the dysmorphology exam.

2.2 | Study design and data collection

Women who consented to participate were interviewed by telephone two to three times during pregnancy using a standard questionnaire about their medical history, prescription and non-prescription medication exposures during pregnancy, history of previous pregnancies, family medical history, pre-pregnancy body mass index, and socio-economic and demographic characteristics of the woman and her partner. Exposure history included start and stop dates of each prescription and over-the-counter medication, as well as indications, dosage changes, and frequencies, use of caffeine, dietary supplements, occupational exposures, infections, prenatal testing or other medical procedures, and use of recreational drugs, tobacco, and alcohol.

Birth outcomes were obtained using a standard interview form completed by telephone shortly after delivery. Women were asked about exposure information through the end of pregnancy, the presence or absence of major structural defects, gestational age at delivery, mode of delivery, length and type of hospital stay, maternal or newborn complications, maternal weight gain, and infant birth weight, length, and head circumference.

Medical records from the prenatal care provider, delivery hospital, any specialty providers that managed the woman's care in pregnancy, and the pediatrician were collected and data abstracted for additional exposure and outcome information, including validation of maternal self-report of autoimmune disease diagnosis. In addition, the infant's physician was asked to return a form reporting postnatal growth measures and the presence or absence of any major structural defect noted up to that point.

Live-born infants underwent a blinded physical examination by one of six study dysmorphologists who traveled to examine the infants in their home typically in the first year of life. These evaluations were completed for both major and minor structural anomalies, including IH. If one or more IH(s) were identified on the dysmorphology exam, the examiner frequently noted the size and location of the IH. Minor anomalies were defined as structural defects with no cosmetic or functional importance that are known to occur in <4% of the general population (Marden, Smith, & McDonald, 1964). Infants who received a dysmorphologic examination were evaluated using a standard checklist itemizing 132 such minor anomalies (Chambers et al., 2001). With parental consent, photographs were taken of each infant to aid in addressing possible issues of interrater reliability among multiple examiners. The examiner in each case was blinded with regards to the medication exposure and autoimmune disease status of the mother.

2.3 | Classification of exposure groups

Autoimmune diseases considered in the analysis included the following: (1) Crohn's Disease (CD); (2) Ulcerative Colitis (UC); (3) Rheumatoid Arthritis (RA); (4) Psoriasis (PsO); (5) Psoriatic Arthritis (PsA); and (6) Ankylosing Spondylitis (AS). Maternal report validated by medical records was used to classify maternal autoimmune disease. Women who were

enrolled in the study who met criteria for inclusion in this analysis and had no history of any of the aforementioned autoimmune diseases were selected as a comparison cohort.

Medication treatments for autoimmune diseases were grouped by class and defined as treatment at any dose for any length of time in pregnancy. The specific classes of medications considered included biologics, non-biologic disease modifying anti-rheumatic drugs (DMARDs), and oral glucocorticosteroids.

Disease activity for autoimmune subjects was documented at initial intake and 32 weeks' gestation using the following standardized questionnaires: Health Assessment Questionnaire-Disability Index (HAQ-DI) for rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis, and the Short Inflammatory Bowel Disease Questionnaire (SIBDQ) for Crohn's and UC subjects (Bruce & Fries, 2003; Irvine, Zhou, & Thompson, 1996). HAQ-DI scores ranged from 0–3, and final calculated values ≤0.5 were categorized as "low" disease activity, and scores >0.5 were categorized as "high" disease activity. While there are no widely validated cutoff values for SIBDQ values, calculated SIBDQ scores ranging from 10–30 were categorized as "high" disease activity, and scores ranging from 31–70 were categorized as "low" disease activity, based upon correlations between SIBDQ scores and disease severity observed in a study by Jowett, Seal, Barton, & Welfare, 2001.

2.4 | Covariates

Baseline covariates considered in the analysis included the following: maternal age in years at the time of conception, parity and gravidity at the time of conception, pre-pregnancy body mass index (BMI), maternal race, maternal Hispanic ethnicity, education level, and household income. Outcomes considered as covariates in the analysis included the following: preeclampsia, preterm delivery, infant sex, birth weight, and whether the infant was a product of multiple gestation (i.e., a twin or higher order multiple). Multiple gestation was further defined as a pregnancy with more than one fetus identified during prenatal care, regardless of whether all fetuses resulted in live births. Preterm delivery was defined as delivery at less than 37 completed weeks' gestation regardless of mode of delivery or indication; low birth weight (LBW) was defined as less than 2,500 g regardless of sex of the infant or gestational age at delivery, and very low birth weight (VLBW) was defined as less than 1,500 g.

2.5 | Statistical analyses

Maternal characteristics were compared by presence or absence of IH in the infant using two-tailed univariate comparisons with Student's *t*-test for continuous variables and Fisher's Exact Test or χ^2 tests for categorical variables, depending on the cell size. Next, the odds ratios of IH were estimated by maternal autoimmune status. The sample was further limited to autoimmune cases, and the odds of IH were then calculated for disease activity. Lastly, odds of IH were calculated for categories of medication use (biologic medication as compared to non-biologic medication or no medication use, biologic medication alone as compared to DMARD alone, and DMARD treatment compared to no medication use).

Pregnancies that ended with more than one live-born infant were counted as separate events with respect to IH. Numbers of IH events were too limited to perform multivariable analysis

or analysis based on size of the tumor; however, the distribution of IH by size was described within categories of infant sex, medication use, and maternal autoimmune disease. Size of IH was classified into three groups: ≤1 × 1 cm, >1 × 1 cm to <3 × 3 cm, and ≥3 × 3 cm. If more than one hemangioma was present, the larger lesion was classified according to size. A lesion that was considered large or of medical significance was classified as a major malformation using the US Centers for Disease Control and Prevention criteria. Despite IH not being typically present at birth, the term "birth prevalence" was used when referencing these malformations instead of "incidence" as part of standard practice, given the possibility that many of these anomalies may be lost prior to pregnancy recognition.

A *p*-value cut-off of 0.05 was considered statistically significant. No adjustment for multiple comparisons was performed. All analyses were conducted using Statistical Package for the Social Science(SPSS) statistical software Version 22.0 (2013), or Version 23.0 (2015; Armonk, NY).

3 | RESULTS

A total of 1,209 infants born to 1,175 women met study inclusion criteria. Baseline characteristics of the maternal population are outlined in Table 1. When categorized by presence or absence of IH in the infants, maternal age was comparable (32.32 ± 5.07 vs. 32.72 ± 4.74 years), as was pre-pregnancy BMI, mean gravidity and parity, ethnicity, education level, household income, and race. None of the other risk factors previously reported in the literature was statistically significantly associated with IH in this sample, specifically LBW, preterm delivery, preeclampsia, female infants, or multiple gestation infants (Table 1).

The most predominant autoimmune disease in the OTIS cohort was RA at 52.8% of the entire autoimmune population, followed by CD(22.6%), PsO (20.3%), PsA (10.5%), AS (8.4%), and UC (3.6%) (data not shown).

The overall birth prevalence of an infant with any one or more IH was 59/1209 or 4.9% (95%CI 3.66–6.09). When examining by maternal autoimmune status, 51/969 (5.3%) were born to mothers with an autoimmune disease, and 8/240 (3.3%) were born to mothers without any autoimmune disease (OR in the autoimmune group, 1.61; 95%CI, 0.75–3.44). There was a statistically significant association between the presence of UC in the mother and development of IH in the child as compared to infants born to mothers without autoimmune disease (OR in the UC group, 3.46; 95%CI, 1.29–9.26). No other specific autoimmune condition was significantly related to IH in any of the comparisons (Table 2).

A total of 618 subjects, 31 of whom had IH, and 464 subjects, 26 of whom had IH, completed the HAQ-DI questionnaire at intake and 32 weeks, respectively. 160 subjects, 8 of whom had IH, and 148 subjects, 8 of whom had IH, responded to SIBDQ at intake and 32 weeks, respectively. Univariate analysis between presence of IH and disease severity did not reveal any statistically significant associations, aside from a borderline protective effect for HAQ-DI at 32 weeks (OR 0.39; 95%CI, 0.15–0.99) (Table 3).

With respect to maternal treatments, as shown in Table 4, there were no significant differences in the rates of IH by medication class. When compared to non-biologic medication use (use of DMARDs and/or steroids), a higher odds of IH was seen in the biologic group, but this was not statistically significant (OR 2.70; 95%CI, 0.83–8.84). The birth prevalence was similar for those on biologic treatment as compared to no medication use (OR in the biologic group, 1.18; 95%CI, 0.41–3.38). Only one case of IH was observed in infants born to mothers who used DMARDs without concomitant biologic or steroid therapy.

Of the 59 infants with IH, 46 had the lesion(s) size documented. Five had a clinically significant lesion that was at least 3 cm in diameter. Four of these five infants were female, all five infants were born to mothers in the autoimmune group (2 RA, 1 RA, and CD, 1 CD alone, 1 PsA), and all five mothers were taking a biologic medication during pregnancy (Table 5). Of note, four of the five mothers of an infant with large IH took a biologic medication through the third trimester of their pregnancy (data not shown).

4 | DISCUSSION

The overall birth prevalence of IHs in this cohort (4.9%) was consistent with that estimated of the general population. Preterm delivery, LBW infant, female infant, and multiple gestations, which are all known predictors of IH, were not significantly associated with IHs in our cohort (Abdul Sultan et al., 2016; Langen et al., 2014; Lin et al., 2010; Shand et al., 2016). The overall birth prevalence of IH in children born to women with autoimmune disease was higher than IHs in children born to healthy comparison women (5.3% compared to 3.3%, respectively), but was not statistically significant.

While an association with other autoimmune diseases is possible, in this study only maternal UC was found to be significantly associated with infant IH. This newfound association between IHs and UC may provide insight into IH pathogenesis. IHs have traditionally been regarded as tumors of microvessels in the infant, but more recent evidence supports the idea that IH lesions may in fact originate from PCVMCCs that have embolized to the developing fetus during the first trimester (Itinteang et al., 2011). The subsequent cellular proliferation of IHs during early infancy has been linked to maternal events associated with hypoxic stress as well as hypoxia-induced factors in the infant (Smith, Friedlander, Guma, Kavanaugh, & Chambers, 2017). The HIF-1a cascade and its downstream targets have been repeatedly implicated in IH development (de Jong et al., 2016). Glucose transporter-1 (GLUT-1), a marker of glucose metabolism and a downstream target of HIF-1a, has been shown to be universally expressed in IH tissue (de Jong et al., 2016; North et al., 2001). In a recent study by El-Raggal et al. (2017) vascular endothelial growth factor (VEGF), another product of the HIF-1a cascade, was observed in significantly higher levels in the sera of IH patients than those with other vascular malformations (2017).

Interestingly, tissue hypoxia may also have an important impact on inflammatory signaling in IBD (Biddlestone, Bandarra, & Rocha, 2015; Cummins, Keogh, Crean, & Taylor, 2016). One study by Xu and Dong (2016) found increased amounts of HIF-1a in the sera of UC patients correlating with disease activity (2016). GLUT-1, the downstream target of HIF-1a

that is strongly associated with IH, has been detected in the colonic epithelia of patients with UC (Fogt et al., 2001). Furthermore, VEGF may also play an important role in the angiogenesis and intestinal inflammation seen in IBD (Scaldaferri et al., 2009). Hypoxia-induced factors are thus an intrinsic component of both IH pathogenesis and UC inflammatory signaling.

In this study, maternal biologic use was not significantly associated with development of IH in the infant. Overall the frequency of IH was higher in infants born to mothers taking biologic therapy at any time in pregnancy than seen in the comparison groups, but none of the comparisons achieved statistical significance. Our study is not the first to assess risk of maternal use of biologic medications on potential fetal birth defects. A prospective cohort study by Weber-Schoendorfer et al. (2015) analyzed pregnancy outcomes in 495 tumor necrosis factor inhibitor-exposed pregnancies, about half of whom had IBD, and identified four of the twenty one major defects seen as IHs (2015). These included two of nine major defects in an adalimumab-exposed group, and two of seven major defects in an infliximab-exposed group, the former two cases indicated for AS and the latter two indicated for Crohn's and UC. While we did not conclude in our study that any maternal autoimmune disease treatment or the overall presence of autoimmune disease itself was associated with IH, we did note a clustering of larger IH in infants born to mothers who had autoimmune disease and who were treated with biologics (100% of those five IH ≥ 3 × 3 cm). These clinically relevant cases of IH occurred entirely within the autoimmune disease cohort and in infants born to women taking biologic medications during their pregnancy, particularly in the third trimester. This finding, along with the results from the Weber-Schoendorfer et al. (2015) study, suggest that a link between autoimmune disease, biologic use, and IH may exist, especially with regards to the size and medical significance of IHs.

PCVMCCs as a possible origin of IHs leads one to question the nature of the maternal placental environment in utero. Maternal inflammation and stress during pregnancy from conditions like UC, as well as biologic exposure, may affect the placental environment in such a way that the offspring is predisposed to IH development. The association between IH and maternal UC seen in this study would support this hypothesis. Furthermore, our study would suggest that perhaps the placental environment and biologic exposure in utero is relevant to IH development beyond the first trimester.

Disease activity measures were included in this study given the potential for confounding, as maternal disease and disease activity have the potential to directly affect choice of medication in the mother. Similarly, maternal disease activity may also impact the incidence of preterm delivery, LBW infants, and other covariates analyzed in this study, as higher disease activity has been shown to correlate with these perinatal outcomes (Atta et al., 2016; Kammerlander et al., 2017). In our study, no association was identified between the presence of IH and maternal disease activity measures collected at intake, although a borderline protective effect was seen with HAQ-DI at 32 weeks. The latter finding is based on an unadjusted analysis with small numbers, however, and may have been influenced by the fact that higher disease activity may be seen in patients not taking disease-modifying medications. Regardless, more research is necessary to tease out the potential relationship between disease activity on IH.

The relatively small number of infants with IH was a limitation of this study, limiting statistical power to detect more modest differences between groups, to allow for classification of medication use by gestational timing and dose, or to allow for multivariable adjustment. No adjustment for multiple testing was performed, and given the large number of comparisons, it is possible that some of our findings may have been due to chance alone. Another limitation of the disease activity analysis is that all measures were collected during pregnancy and not necessarily prior to initiation of treatment, so the temporality between disease severity and treatment was not evaluated. Furthermore, disease activity measures were not available for those in the sample with psoriasis alone.

A strength of the study was the standardized and specialized blinded physical examination conducted for all infants. This ensured that the IH(s) that were still present in the infant would be uniformly detected, and that the exact sizes and locations of the IH(s) could be noted, which is pertinent to clinical implications. Some of the IH lesions (13 out of 59) did not have specific size or location noted by the examiner. However, none of these lesions were considered major malformations and thus were presumably of smaller size and with less clinical significance. Lastly, despite similar timing of dysmorphological evaluations performed in the autoimmune and comparison cohorts, it is possible that some infants with an IH were not detected, as the lesion may have already regressed by the time the child was evaluated.

The results of this study add to the limited knowledge regarding birth outcomes and presence of IHs in the autoimmune population. Further and larger studies would be warranted to continue investigating the potential association between maternal presence of autoimmune disease, particularly UC, and infant development of IH.

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TABLE 1

Characteristics among women and infants in OTIS cohort 2004–2013 by presence/absence of infantile hemangioma (IH)

Characteristic	Hemangioma *N* = 59	Non-hemangioma *N* = 1150	*p*-value[a]
Maternal age at estimated due date—mean (standard deviation)	32.32 (5.07)	32.72 (4.74)	0.548
Gravidity—mean (standard deviation)	1.97 (1.20)	2.24 (1.54)	0.093
Parity—mean (standard deviation)	0.54 (0.84)	0.72 (0.98)	0.122
Pre-pregnancy body mass index category—kg/m2—mean (standard deviation)[b]	24.26 (4.73)	25.00 (5.85)	0.250
Preeclampsia—*n* (%)	2 (3.4)	58 (5.0)	0.764
Preterm delivery (<37 weeks' gestation)—*n* (%)	10 (16.9)	172 (15.0)	0.817
Infant sex, female - *n* (%)	35 (59.3)	543 (47.2)	0.093
Multiple births category—*n* (%)	5 (8.5)	76 (6.6)	0.589
Infant birth weight—*n* (%)			
Low	8 (13.6)	105 (9.1)	0.416
Very low	0	18 (1.6)	1.000
Race—*n* (%)[c]			
White	55 (93.2)	960 (85.3)	
Black	0	34 (3.0)	
Asian/Pacific Islander	1 (1.7)	34 (3.0)	0.319
Native American	1 (1.7)	5 (0.4)	
Other	0	6 (0.5)	
Unable to code	2 (3.4)	87 (7.7)	
Ethnicity—*n* (%)[d]			
Non-hispanic	49 (96.1)	813 (88.6)	0.151
Hispanic	2 (3.9)	105 (11.4)	
Education—*n* (%)			
Less than 9th grade	0	5 (0.4)	
Junior high school	0	8 (0.7)	
Partial high school	0	10 (0.9)	0.118
High school graduate	3 (5.1)	64 (5.6)	
Some college	8 (13.6)	239 (20.8)	
College/university graduate	36 (61.0)	457 (39.7)	
Post-college graduate	12 (20.3)	367 (31.9)	
Household income—*n* (%)[e]			
<$10,000	1 (1.7)	23 (2.0)	
$10,000–$49,999	6 (10.3)	182 (16.1)	0.291
>$50,000	48 (82.8)	901 (79.6)	
Unknown	3 (5.2)	26 (2.3)	

[a] Two-sample t-test for continuous variables, χ^2 test or (Fisher's Exact Test where expected number in cell <5) for categorical variables.

[b] Pre-pregnancy Body Mass Index Category—kg/m2 missing for 1 subject in the Non-Hemangioma Group.

[c] Race missing for 24 subjects in the Non-Hemangioma Group.

[d] Ethnicity missing for 8 subjects in the Hemangioma Group, and 232 subjects in the Non-Hemangioma Group.

[e] Household Income missing for 1 subject in the Hemangioma Group, and 18 subjects in the Non-Hemangioma Group.

TABLE 2

Infantile Hemangioma by disease category in OTIS cohort 2004–2013

Characteristic	*N*	Hemangioma *N* = 59[a] *N* (%)	Odds ratio (95%CI)[b]
Any autoimmune disease[c]	969	51 (5.26)	1.61 (0.75–3.44)
Ankylosing spondylitis	81	3 (3.70)	0.74 (0.23–2.41)
Crohn's disease	219	12 (5.48)	1.16 (0.61–2.23)
Psoriasis	197	7 (3.55)	0.68 (0.30–1.52)
Psoriatic arthritis	102	5 (4.90)	1.01 (0.39–2.57)
Rheumatoid arthritis	512	28 (5.47)	1.24 (0.74–2.10)
Ulcerative colitis	35	5 (14.29)	3.46 (1.29–9.26)

[a] Eight IH were present in women without autoimmune disease (*N* = 240, 3.33%).

[b] Unadjusted odds ratio is presented with 95% confidence interval.

[c] Subjects may have used more than one classification in these categories, resulting in column sums >100%.

TABLE 3

Influence of maternal active autoimmune disease (HAQ-DI>0.5 or SIBDQ score 10–30) compared to inactive disease (HAQ-DI ≤ 0.5 or SIBDQ score 31–70) on presence of infantile hemangioma (IH) in infants

	Active disease			Inactive disease			
Autoimmune disease, score[a]	**N**	**No. IH**	**%**	**N**	**No. IH**	**%**	**Odds Ratio (95%CI)[b]**
HAQ-DI, intake	215	9	4.19	403	22	5.46	0.76 (0.34–1.67)
SIBDQ, intake	136	7	5.15	24	1	8.33	1.25 (0.15–10.63)
HAQ-DI, 32 weeks	196	6	3.06	268	20	7.46	0.39 (0.15–0.99)
SIBDQ, 32 weeks	133	7	5.26	15	1	6.67	0.78 (0.09–6.79)

Data from OTIS cohort 2004–2013 (N = 969).

[a] Thirty one subjects with IH and 587 without IH responded to HAQ intake; 8 subjects with IH and 152 without IH responded to SIBDQ at intake; 26 subjects with IH and 438 without IH responded to HAQ at 32 weeks; 8 subjects with IH and 140 without IH responded to SIBDQ at 32 weeks.

[b] Unadjusted odds ratio is presented with 95% confidence interval; HAQ-DI, Health Assessment Questionnaire-Disability Index; SIBDQ, short inflammatory bowel disease questionnaire.

TABLE 4

Infantile hemangioma (IH) among infants born to women with autoimmune disease (*N* = 969) by autoimmune treatment class in OTIS cohort 2004–2013

	Medication treatment class			Comparison treatment class			Odds ratio (95%CI)[a]
	N	No. IH	%	N	No. IH	%	
Biologic use							
Any biologic use versus non-biologic medicine use (DMARDs, steroids)	760	44	5.80	135	3	2.22	2.70 (0.83–8.84)
Any biologic use versus no medication use	760	44	5.80	77	4	5.19	1.18 (0.41–3.38)
Biologic use alone versus DMARD use alone	397	26	6.55	37	1	2.70	2.52 (0.33–19.14)
DMARD use							
Any DMARD use versus no medication use	213	6	2.82	77	4	5.19	0.53 (0.15–1.93)

[a]Unadjusted odds ratio is presented with 95% confidence interval; DMARD, disease modifying anti-rheumatic drug.

TABLE 5

Breakdown of infantile hemangioma size by infant sex, maternal medication class and by specific autoimmune disease in OTIS cohort 2004–2013 (N = 1209)

	Infantile hemangioma size (cm)				
	≤1 × 1	**>1 × 1, <3 × 3**	**≥3 × 3**	**Unknown**	**Not present**
	***n* = 19**	***n* = 22**	***n* = 5**	***n* = 13**	***n* = 1,150**
	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**
Female infant (n = 578)	9 (47.4)	14 (63.6)	4 (80.0)	8 (61.5)	543 (47.2)
Medications					
Any biologic use (n = 760)[a]	16 (84.2)	13 (59.1)	5 (100.0)	10 (76.9)	716 (62.3)
Any DMARD use (n = 213)[a]	1 (5.3)	3 (13.6)	1 (20.0)	1 (7.7)	207 (18.0)
Steroid use (n = 406)	5 (26.3)	9 (40.9)	2 (40.0)	4 (30.8)	386 (33.6)
Autoimmune disease[a]					
Any autoimmune disease (n = 969)	18 (94.7)	17 (77.3)	5 (100.0)	11 (84.6)	918 (79.8)
Ankylosing spondylitis (n = 81)	1 (5.3)	1 (4.5)	0 (0.0)	1 (7.7)	78 (6.8)
Crohn's disease (n = 219)	4 (21.1)	3 (13.6)	2 (40.0)	3 (23.1)	207 (18.0)
Psoriasis (n = 197)	2 (10.5)	2 (9.1)	1 (20.0)	2 (15.4)	190 (16.5)
Psoriatic arthritis (n = 102)	2 (10.5)	1 (4.5)	1 (20.0)	1 (7.7)	97 (8.4)
Rheumatoid arthritis (n = 512)	10 (52.6)	10 (45.5)	3 (60.0)	5 (38.5)	484 (42.1)
Ulcerative colitis (n = 35)	3 (15.8)	2 (9.1)	0 (0.0)	0 (0.0)	30 (2.6)

[a]Subjects may have used more than one classification in these categories, resulting in column sums >100%.