Perinatal characteristics, maternal reproductive history and juvenile idiopathic arthritis: A case-control study

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Abstract

Background: Juvenile Idiopathic Arthritis (JIA) is a heterogeneous group of chronic inflammatory arthritis conditions in children with onset before 16 years of age, and is the leading cause of acquired short and long-term disability in childhood. The etiology of JIA is largely unknown, however there is increasing evidence that autoimmune diseases, including JIA, may be associated with maternal reproductive or early childhood exposures.

Methods: We conducted a case-control study of JIA cases identified at a regional children's hospital in the Seattle-Puget Sound area, using linked birth certificate data from 1987 - 2009. Potential cases included all children <20 years with relevant ICD codes who had received inpatient or outpatient care. Their records were linked to Washington State birth records for 1980-2009 to identify those with a Washington State birth certificate (N=1,518). For comparison, control children were randomly selected in a ratio of 4:1 from the remaining birth records, frequency matched on year of birth (N=6,072). Review of medical records further refined case ascertainment based on specific clinical criteria (N=1,254) and allowed categorization of cases into JIA subtypes. Multivariable logistic regression was used to estimate adjusted odds ratios (OR) and 95% confidence intervals (CI) for the associations of JIA/JIA subtypes with maternal and early life exposures as measured in the birth certificates.

Results: Decreased ORs were observed for JIA in relation to greater maternal parity (2 prior live births, OR 0.70, 95% CI 0.58, 0.85; 4+ prior live births, OR 0.68, 95% CI 0.48, 0.97), a finding also observed for the persistent oligoarticular JIA subtype. Fewer cases (11.4%) than controls (13.3%) had a birth weight >4000 g (OR 0.81, 95% CI 0.67, 0.98). Mothers of cases (5.2%) were slightly more likely than those of controls (4.1%) to have had preeclampsia during their pregnancy (OR 1.29, 95% CI 0.96, 1.73).

Discussion: To our knowledge, no studies to date in the United States have examined these exposures in relation to JIA. Greater maternal parity, specifically having 2 or more prior live births, was significantly associated with a decreased OR for JIA, a finding consistent with both the hygiene and microchimerism hypotheses.

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Introduction

Juvenile Idiopathic Arthritis (JIA) is a heterogeneous group of chronic inflammatory autoimmune diseases in children with onset before 16 years of age, and is the leading cause of acquired short and long-term disability in childhood (Petty 2004). JIA has an approximate incidence of 4 per 100,000 per children per year in the United States (Cassidy 2011). There are 7 recognized subtypes, including rheumatoid factor (RF) positive polyarticular, RF negative polyarticular, persistent oligoarticular or extended oligoarticular, systemic, psoriatic, enthesitis-related (ERA), and other undifferentiated arthritis (Petty 2004). Oligoarthritis is the most common type of JIA in North America, which affects fewer than 5 joints; RF positive polyarthritis is the least common and affects 5 or more joints (Cassidy 2011). JIA likely has a complex etiology, with multiple genetic and environmental factors contributing to an autoimmune reaction. All subtypes likely involve activated T cells and macrophages in the pathogenesis of disease (Cassidy 2011).

The pathogenesis likely differs from one onset type to another. Systemic arthritis is not characterized by autoantibodies or a strong genetic predisposition whereas the pathogenesis of both oligoarthritis and RF positive polyarthritis suggest that the humoral immune system plays a central role. Antinuclear (ANA) antibodies are common in patients with oligoarthritis, and IgM rheumatoid factor levels are increased in patients with RF positive polyarthritis. In addition to RF, the presence of anti-citrullinated protein antibody (CCP) is associated with disease severity. In contrast, ERA, RF negative polyarthritis, and psoriatic arthritis are less likely to produce autoantibodies, and have strong associations with polymorphisms at the histocompatibility locus. The subtype ERA is strongly associated with HLAB27 polymorphism at the histocompatibility locus (Cassidy 2011).

Exposures during pregnancy and the *in utero* environment have been associated with several adult diseases among offspring (Phillips 2006). It is now known that the fetus responds to environmental factors, a process known as developmental plasticity (Phillips 2006). There is increasing evidence that birth weight and gestational length reflect the quality of the intrauterine environment, since prenatal factors influence growth and are also associated with diseases later in life (Phillips 2006). Maternal parity may influence the risk of autoimmune disease, including JIA (Phillips 2006, Jacobsson 2003, Stene 2004). Concordance rates of JIA among monozygotic twins are estimated in the range 25-40%; this low concordance suggests that environmental factors may greatly influence JIA risk (Ellis 2009).

Currently, two major hypotheses have been suggested relating perinatal and maternal reproductive characteristics to JIA. First, the "hygiene hypothesis" suggests that exposure to infections in early life may result in a decreased risk of autoimmune diseases during childhood (Yazdanbakhsh 2002; Bach 2002) because of a modulation of the developing immune system. The second hypothesis relates to maternal and/or sibling origin microchimerism. Microchimerism refers to the harboring of cells (or DNA) from another individual. This results from the exchange of cells or DNA from genetically distinct individuals, which may be acquired *in utero* from the mother or older siblings during gestation (Gammill 2010; Nelson 2012; Maloney 1999). Microchimerism could potentially affect the risk of disease because the microchimerism could have genes that are protective or increase the risk of disease (Rak 2009; Yan 2011).

The etiology of JIA is largely unknown, however there is increasing evidence that adult onset rheumatoid arthritis (Jacobson 2003, Colebatch 2010), some autoimmune diseases (D'Angeli 2010;Phillips 2006), and other chronic adult conditions (Nijland 2008) are associated with

maternal reproductive or early childhood exposures. Developmental factors may also be relevant for JIA. We conducted a case-control study using birth certificates linked to JIA data from a regional children's hospital to explore the associations of selected maternal reproductive and infant characteristics in relation to JIA. Elucidation of these relationships will provide a better understanding of possible *in utero* risk factors for JIA, aid in the development of interventions, and help us understand the etiology of this complex autoimmune disease.

Methods

Study Design

We conducted a case-control study of JIA cases identified at a regional children's hospital, a major medical facility in the Seattle-Puget Sound region of Washington State, using linked birth certificate data from 1980 - 2009. Potential cases included all children < 20 years old with an *International Classification of Diseases, Ninth Revision* code for JIA (720.0, 696.0, 714.32, 714.31, 714.30, 720.89, 714.33, 714.3) who were treated at Seattle Children's Hospital and Medical Center (SCHMC) during 1987 – 2010, as identified by screening the facility's inpatient and outpatient registers (N=2,274). The records of potential cases were linked to Washington State birth records for 1980-2009 to identify children born in the state and for whom a birth certificate was identified (N=1,518). For comparison, control children were randomly selected in a ratio of 4:1 from the remaining birth records, frequency matched on year of birth (N=6,072).

Additional case information abstracted from medical records included JIA subtype, age at onset, age at diagnosis, and serologic status, rheumatoid factor (RF), anti-nuclear antibody (ANA), anti-citrullinated protein antibody (CCP), and HLA-B27. The subtypes included: polyarticular arthritis RF positive, polyarticular arthritis RF negative, persistent oligoarticular arthritis,

extended oligoarticular arthritis, psoriatic arthritis, enthesitis related arthritis, systemic arthritis, and undifferentiated arthritis. Cases were further confirmed by review of their medical record; 226 were excluded because they did not meet the International League of Associations for Rheumatology (ILAR) criteria, (Petty 2004) for a diagnosis of JIA and 38 were excluded due to disease onset at > 16 years of age, resulting in 1,254 total JIA cases for analyses.

Exposure information was obtained from subjects' birth records, including infant and maternal reproductive characteristics. Infant characteristics included birth weight, size for gestational age (SGA), and gestational age at delivery. Low birth weight was defined as less than 2500g and high birth weight was defined as greater than 4000g. Size for gestational age (SGA) was defined as small for gestational age as birth weight below the 10^{th} percentile for the infant's gestational age and sex and large for gestational age as birth weight in the upper 10^{th} percentile calculated using Washington State data 1989 – 2002 as a standard, calculated from the clinical estimate of gestational age indicated on the birth certificate. Preterm delivery and post-term delivery were defined as delivery at < 37 weeks and > 42 weeks gestation, respectively.

The infant and maternal reproductive characteristics relevant to the hygiene hypothesis included number of prior births, mode of delivery (vaginal or cesarean section), and plurality – twin or higher order. To examine the microchimerism hypothesis, in addition to birth order, plurality, and mode of delivery, number of prior fetal losses less than 20 weeks' or greater than 20 weeks' gestation were also examined.

Statistical Analysis

Risk estimates were first evaluated using stratified analyses. Subsequently, multivariate logistic regression was used to estimate the odds ratio (OR) estimates of the relative risks and 95%

confidence intervals (CIs) for the associations of interest. Levels of missing data were generally similar for cases and controls; the level of missing data for all infant variables were less than 5%, except for SGA, which had 13-15% missing. Missing data levels for maternal reproductive variables were less than 10%, except for the fetal loss variables, which were missing 13% (<20 weeks gestation) and 15% (>=20 weeks gestation). Not all variables were available for all years, including maternal education, maternal alcohol consumption during pregnancy, health insurance status, and trimester of inception of prenatal care; missing data levels ranged from 8% - 40% for these. Subjects with missing data were excluded from relevant analyses.

All ORs were adjusted for maternal age and the frequency-matching variable, birth year. Factors that were evaluated for their potential effects on the relationships of interest included maternal age, paternal age, race, educational level, marital status, medical insurance (Medicaid vs. other) at the birth hospitalization, prenatal smoking, alcohol use during pregnancy, infant sex, and trimester of inception of prenatal care. If adjustment for these variables changed ORs by more than 10%, they were considered as confounders and retained in the relevant risk estimates. Potential effect modifiers were evaluated by inspection of stratum-specific risk estimates for important differences and the Breslow-Day test for homogeneity. Possible trends were evaluated using a Wilcoxon rank sum test. Analyses were conducted using Stata software (version 11; StataCorp, College Station, Texas). Appropriate institutional review board approvals were obtained prior to study conduct.

Results

Characteristics of JIA cases and controls

A greater proportion of cases (67.3%) than controls (47.8%) were female [table 1]. Mothers of cases were more likely to be older, married, of higher education level, and white. Fathers of cases were also slightly more likely (26.7%) than those of controls (22.9%) to be 35 years or older. [table 1].

Characteristics of the JIA cases

The mean age at diagnosis for verified JIA cases was 8.9 years and the mean age at onset was 7.9 years [table 2]. The most prevalent JIA subtype was persistent oligoarticular arthritis (31.4%), followed by enthesitis related arthritis (21.4%), RF negative polyarticular arthritis (18.7%), extended oligoarticular arthritis (5.8%), systemic arthritis (5.7%), psoriatic arthritis (5.0%), RF positive polyarticular arthritis (4.8%), polyarticular arthritis with unknown RF status (3.9%), and undifferentiated arthritis (3.1%) (data not shown).

Perinatal factors in relation to JIA

Fewer cases (11.4%) than controls (13.3%) were high birth weight (OR: 0.81, 95% CI: 0.67, 0.98) [table 3]. Post-term delivery was associated with a modestly decreased risk (OR: 0.88, 95% CI: 0.70, 1.10) of JIA. None of the other perinatal factors and infant characteristics were associated with significantly increased or decreased risks of JIA.

Perinatal factors in relation to JIA subtypes

To the extent possible, we examined these same factors for their potential associations with each JIA subtype. In all subtypes, except RF negative polyarticular JIA and enthesitis related JIA, fewer cases than controls were high birth weight, although the ORs were not statistically significant for either of the subtypes (data not shown). In all subtypes, except extended oligoarticular JIA and undifferentiated JIA, we observed that fewer cases than controls were born

post-term, although again, results were not statistically significant for either subtype. We observed that RF positive polyarthritis cases (13.8%) were more likely to be born pre-term, than were controls (6.6%) (OR, 2.11, 95% CI: 0.99, 4.53). Enthesitis related arthritis cases (11.2%) compared to controls (6.6%) were similarly more likely to be born pre-term (OR, 1.73, 95% CI: 1.16, 2.60). Undifferentiated arthritis cases (23.5%) as compared to controls (9.6%) were more likely to be small for gestational age (OR, 2.74, 95% CI: 1.23, 6.12) (data not shown).

Reproductive factors in relation to JIA

Relative to having no prior live births, infants of women with 2 or more prior births had reduced risks of JIA (2 live births, OR, 0.70, 95% CI: 0.58, 0.85, 3 live births, OR, 0.69, 95% CI: 0.52, 0.93, 4 or more live births, OR, 0.68, 95% CI: 0.48, 0.97, p for trend <0.05) [table 3]. Among all subjects, cases (21.5%) were slightly more likely than controls (19.0%) to have had a cesarean delivery (OR, 1.10, 95% CI: 0.95, 1.28). Mothers of cases (5.2%) were slightly more likely than those of controls (4.1%) to have preeclampsia during the index pregnancy (OR, 1.29, 95% CI: 0.96, 1.73). Prior maternal fetal loss was not associated with increased or decreased ORs for JIA.

Reproductive factors in relation to JIA subtype

Among persistent oligoarthritis cases, relative to having no prior live births, infants of women with 1 or more prior births had reduced risks for the association with JIA (4 or more births, OR, 0.32, 95% CI: 0.14, 0.69). Among systemic arthritis, RF negative polyarthritis, extended oligoarthritis, and undifferentiated arthritis cases, similar associations were seen, although not significant. However, among RF positive polyarthritis relative to having no prior live births, infants of women with 4 or more prior births had an increased OR for the association (OR, 3.58, 95% CI: 1.33, 9.57). Among enthesitis related arthritis cases, relative to having no prior live

births, infants of women with 1 prior birth had an increased OR for the association with JIA (OR, 1.37, 95% CI: 1.02, 1.83) (data not shown).

Mothers of infants with RF positive polyarthritis were more likely to have had a cesarean section than controls (OR, 1.78, 95% CI: 1.0, 3.18). Among undifferentiated JIA cases, mothers of cases (13.5%) were more likely than controls (4.1%) to have had preeclampsia (OR, 4.17, 95% CI: 1.6, 10.9). Among RF negative polyarthritis cases, mothers of cases (38.0%) compared to controls (30.0%) were more likely to have had at least 1 prior fetal loss <20 weeks' gestation (OR, 2.21, 95% CI: 1.52, 3.20). Among psoriatic arthritis cases, mothers of cases (42.2%) as compared to controls (30.0%) were more likely to have had at least 1 prior fetal loss <20 weeks' gestation (OR, 2.62, 95% CI: 1.44, 4.79). Among enthesitis related arthritis cases, mothers of cases (30.8%) were slightly more likely than controls (30.0%) to have had 1 or more prior fetal losses <20 weeks' gestation (OR, 1.56, 95% CI: 1.13, 2.14) (data not shown).

Discussion

We observed that some perinatal factors and maternal reproductive factors were associated with JIA. High birth weight was significantly associated with decreased risk for JIA. Greater maternal parity was both significantly associated with decreased risks for JIA. To our knowledge, no studies to date in the United States have examined these exposures in relation to JIA.

Prior studies examined infant and mothers' reproductive characteristics in relation to JIA with mixed results; some reported higher rates of pregnancy complications in mothers of children with JIA as compared to controls (Chaudhari 2006), others found low birth weight and small for gestational age associated with reduced risk of JIA (Carlens 2009), whereas others did not find any associations with infant or maternal reproductive characteristics (Berkun 2010). Studies of

autoimmune diseases such as type 1 diabetes indicate there may be an association between maternal environmental factors during pregnancy and later disease onset (Carlens 2009; D'angeli 2010).

An earlier case-control study examining mother's reproductive history and risk of JIA employed a mail survey assessing pregnancy outcomes among mothers of children with JIA (n=227) and best-friend controls (n=235). Mothers of children with JIA had a greater total number of pregnancies and rates of pregnancy loss, and had proportionately more preterm deliveries than mothers of controls (Chaudhari 2006).

We observed that greater maternal parity, specifically having 2 or more prior live births, was significantly associated with a decreased risk for JIA. This was also observed in the persistent oligoarticular JIA subtype, the largest JIA subtype. Similar patterns were seen in the other subtypes as well, although results were not statistically significant, possibly due to small numbers of cases in each category. However, this was not consistent in all subtypes – RF positive polyarthritis and enthesitis-related arthritis had significant increased risks of JIA. This is consistent with both the hygiene and microchimerism hypotheses. Children with older siblings have a greater opportunity to be exposed to infections, either *in utero* or during early post-natal life. The observed association might also be attributed to maternal and/or sibling microchimerism. If the presence of acquired microchimerism carries JIA- protective HLA alleles (generally more prevalent than JIA-risk associated HLA alleles) from an older sibling, then we would expect to see a decreased risk of JIA in relation to higher birth order or greater maternal parity (Feitsma 2007). We also observed increased risks of the association between fetal losses <20 weeks' gestation and among the subtypes: RF negative polyarticular JIA, psoriatic JIA, and enthesitis related JIA. The observed associations might be attributed to maternal and/or sibling

microchimerism if the presence of acquired microchimerism carries JIA-associated risk HLA alleles (Rak 2009; Yan 2011), although chance associations cannot be ruled out.

High birth weight has been reported to be positively associated with adult onset rheumatoid arthritis (Colebatch 2010), however, we found the reverse for JIA. Berkun et. al (2010) reported no associations of infant birth weight with JIA. We also observed that mothers of infants diagnosed with JIA were slightly more likely to have preeclampsia, a finding of borderline statistical significance. Further, we observed that mothers of infants diagnosed with undifferentiated JIA were more likely to have preeclampsia. This may be explained by the high variability in the killer immunoglobulin-like receptor (KIR) gene family and HLA class I – C molecules. KIR is expressed by uterine natural killer (NK) cells, and is in contact with invading fetal placental cells during the first trimester. There is also recent evidence that the KIR B haplotype is associated with protection for preeclampsia and fetal growth restriction. Women who have very large babies may have an increased number of KIR B genes (Chazara 2011). This may at least partly explain our findings, however again, chance associations cannot be ruled out.

A Swedish registry-based, case-control study with >3,000 cases observed that delivery after 42 weeks gestation or by cesarean section were associated with increased risk of onset of JIA after 10 years of age, although no associations with high or low birth weight, number of older siblings and later onset JIA were observed (Berkun 2010). We observed that post-term delivery had a modestly decreased OR and delivery by cesarean section had modestly increased OR, although both results were not statistically significant. We found that delivery by cesarean section had an increased OR association with RF positive polyarticular JIA. We found the reverse for pre-term delivery and risk of JIA in two of the subtypes, RF positive polyarticular and undifferentiated; both were associated with an increased OR.

The use of outpatient and inpatient medical records maintained by board-certified pediatric rheumatologists at a large regional children's medical center, and of data linkage to birth records, are major strengths of this study and facilitated the identification of a relatively large number of cases for a rare disease. Additionally, because exposure information was assessed from birth records prior to onset and diagnosis of JIA, our data is not subject to recall bias. Because of the known polygenic genetic predispositions, disordered immune responses, and heterogeneity of the pathogenesis of differing JIA subtypes, it was important to examine the relationships separately for each subtype. Additionally, because subjects were identified at the sole facility in Washington state with board certified pediatric rheumatologists, our results are probably similar to what would have been observed for a population-based study.

Our study is not without limitations, including possible inaccuracies in the reporting the mother's reproductive history, particularly reporting of fetal loss on the birth certificates. This may lead to non-differential misclassification, possibly biasing the OR estimates towards the null hypothesis. A prior study assessed birth weight, number of prior live births, and maternal and paternal demographics in birth records as reliable in comparison to medical records (Roohan 2003, Zollinger 2006). However, birth certificate data may underestimate prenatal care visits and smoking and alcohol use during pregnancy, thus limiting our ability to evaluate these variables accurately as potential confounders. There is also the potential for unmeasured confounding due to unrecognized pregnancy loss, psychosocial support factors, and our lack of information on fertility. The inability to measure these could lead to residual confounding in our risk estimates and could bias the estimates either way.

Additionally, there is a chance of disease misclassification. The possibility that control subjects may have migrated out of state and been diagnosed elsewhere exists; inclusion of cases among

the controls would, however, bias results towards the null. There are also limitations of using hospital cases. This includes referral bias. The cases at Seattle Children's Hospital may only consist of those with more severe disease. However, as this is the only facility in the region with board - certified pediatric rheumatologists, it is likely that even children with less severe disease were included. This type of bias, if it exists, is unlikely to have an effect on the observed associations. The subtype classification system is continually changing therefore limiting the ability to compare study results over time. Since each subtype varies considerably with respect to clinical and laboratory findings, it is important to examine each group separately, thereby limiting the number of cases in relevant sub analyses.

Given that there are currently no preventative or curative treatments for JIA and that JIA is the leading cause of long-term disability in childhood, further studies are warranted to examine these potential associations, particularly parity, preeclampsia, and high birth weight. A better understanding of these associations will help inform prevention programs and hopefully reduce the burden of this debilitating disease.

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Tables

Table 1. Infant, Maternal, and Paternal Characteristics of JIA Cases and non-JIA Controls born in Washington State 1980- 2009.

	Cases (N=1,254)[a]		Controls (N=6,072)[a]	
	n	%	n	%
Female	844	67.3	2,903	47.8
Race/ Ethnicity				
White	984	81.1	4,425	74.8
Black	37	3.1	316	5.3
A/PI	62	5.1	426	7.2
Native American	38	3.1	150	2.5
Hispanic	91	7.5	598	10.1
Other	1	0.1	3	0.1
Maternal Age (years)				
<20	106	8.5	694	11.4
20-24	234	18.7	1,536	25.3
25-29	385	30.7	1,774	29.2
30-34	342	27.3	1,326	21.9
35+	187	14.9	739	12.2
Paternal Age (years)				
<20	31	2.7	183	3.4
20-24	142	12.2	988	18.3
25-29	304	26.1	1,524	28.3
30-34	375	32.2	1,467	27.2
35+	311	26.7	1,233	22.9
Maternal Race				
White	1,011	84.1	4,638	78.3
Black	24	2.0	233	3.9
A/PI	57	4.7	123	6.8
Native American	33	2.8	402	2.1
Hispanic	77	6.4	526	8.9
Maternal Education (years)				
<12	100	12.9	639	18.0
12	227	29.3	1,092	30.8
12-16	188	24.2	927	26.1
16+	261	33.6	888	25.0
Maternal marital status				
Married	1,002	80.0	4,469	73.9
Unmarried	250	20.0	1,577	26.1
Prenatal care adequacy				
Inadequate	76	10.7	419	12.7
Intermediate	147	20.6	711	21.6
Adequate	319	44.7	1,535	46.6
Adequate Plus	171	24.0	632	19.2

Table 1 continued. Infant, Maternal, and Paternal Characteristics of JIA Cases and non-JIA Controls born in Washington State 1980- 2009.

	Cases (N=1,254)[a]		Controls (N=6,072)[a]	
	n	%	n	%
Trimester of inception of prenatal care				
First	989	85.9	4,591	81.1
Second	133	11.6	897	15.8
Third	29	2.5	175	3.1
No. of prior pregnancies				
None	384	31.4	1,901	32.1
1	370	30.3	1,658	28.0
2	218	17.8	1,111	18.8
3+	251	20.5	1,246	21.1
Smoked Prenatally				
Yes	132	11.3	946	16.8
No	1,032	88.7	4,672	83.2
Alcohol Prenatally				
Yes	14	1.8	93	2.5
No	748	98.2	3,647	97.5
Medicaid billed at delivery				
Yes	283	26.4	1,789	37.0
No	790	73.6	3,043	63.0
Maternal autoimmune disease				
Yes	3	0.2	7	0.1
No	1,257	99.8	6,065	99.9

[a]numbers may not add to total due to missing data

Table 2. Characteristics of JIA cases by subtype born in Washington State 1980-2009.

	RF+ Poly (n=60)		RF - Poly (n=232)		Poly - unknown RF (n=49)		Systemic (n=71)		Oligo (n=390)		Extended Oligo (n=72)		Psoriatic (n=62)		Enthesitis-related (n=266)		undifferentiated (n=39)	
	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD
Age at diagnosis (years)	12.9	3.1	8.0	4.7	8.0	4.3	7.4	4.7	6.8	4.6	5.1	3.4	10.5	4.1	12.3	3.1	11.8	4.0
Age at onset (years)	11.9	3.1	7.1	4.5	7.1	4.2	7.0	4.6	6.1	4.2	4.4	3.0	9.1	3.9	10.7	3.2	10.2	3.8
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Serologic status*																		
Rheumatoid Factor (RF) positive (once)	31	51.7	0	0	N/A		0	0	6	3.3	1	2.8	0	0	5	4.4	3	14.3
Rheumatoid Factor (RF) positive (twice)	29	48.3	0	0	N/A		0	0	0	0	0	0	0	0	0	0	5	23.8
Anti-nuclear antibody positive	35	68.6	121	56.5	12	70.6	8	21.6	192	57.8	46	74.2	25	58.1	60	32.1	12	46.2
HLA-B27 positive	0	0	5	6.3	1	14.3	0	0	12	8.5	1	5.0	0	0	106	49.8	3	11.5
Anti-CCP antibody positive	28	73.7	9	9.8	0	0	0	0	3	8.6	1	5.3	1	7.7	0	0	0	0

*among those with serologic test done

Table 3. Perinatal characteristics and maternal reproductive history exposure among Juvenile Idiopathic Arthritis (JIA) cases and controls born in WA State, 1980-2009.

Exposure information	Cases (N=1,254)		Controls (N=6,072)		Odds Ratio	95% Confidence Interval
Infant Characteristics	n	%	n	%		
Gestation at delivery (weeks)						
<37	81	6.6	389	6.6	1.00	0.78, 1.28
37- 42	1,045	85.0	4,943	83.5	1.00	reference
42+	102	8.3	588	9.9	0.88	0.70, 1.10
Small for gestational age						
<10th percentile	102	9.4	496	9.6	1.01	0.81, 1.27
Normal	992	90.6	4,681	90.4	1.00	reference
Birthweight (g)						
<2500	73	5.8	339	5.6	1.02	0.78, 1.32
2500 - 3999	1,036	82.8	4,912	81.1	1.00	reference
>4000	143	11.4	803	13.3	**0.81**	**0.67, 0.98**
Plurarlity						
Singleton	1,242	98.6	5,989	98.7	1.00	reference
Twin or higher order multiple	18	1.4	79	1.3	1.03	0.62, 1.73
Mother's Reproductive History						
Number of prior births						
0	529	43.3	2,495	42.1	1.00	reference
1	423	34.6	1,916	32.3	0.94	0.82, 1.09
2	166	13.6	953	16.1	**0.70**	**0.58, 0.85**
3	61	5.0	339	5.7	**0.69**	**0.52, 0.93**
4+	44	3.6	228	3.8	**0.68**	**0.48, 0.97**
No. of prior fetal losses (<20 weeks)[1]						
None	513	69.7	2,530	70.0	1.00	reference
1+	223	30.3	1,084	30.0	0.99	0.83, 1.18
No. of prior fetal losses (>20 weeks)[1,2]						
None	714	97.0	3,499	97.0	1.00	reference
1+	22	3.0	107	3.0	1.11	0.69, 1.78
Cesarean Section						
Yes	270	21.5	1,151	19.0	1.10	0.95, 1.28
No	984	78.5	4,916	81.0	1.00	reference
Pre-eclampsia						
Yes	60	5.2	230	4.1	**1.29**	**0.96, 1.73**
No	1,102	94.8	5,410	95.9	1.00	reference

All estimates are adjusted for mom age and birth year.

[1] Estimates are restricted to 839 case mothers and 4,015 control mothers with prior pregnancy

[2] In addition to mom age and birth year, also adjusted for dad age.