Birth Outcomes in Women with a History of Juvenile Idiopathic Arthritis

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ABSTRACT. ***Objective.*** To determine whether children born to women who had juvenile idiopathic arthritis (JIA) had more adverse birth outcomes than children born to mothers who never had JIA.

Methods. Our cohort study used data from physician billing and hospitalizations covering the province of Quebec, Canada. We identified all women with JIA with a first-time birth between January 1, 1983, and December 31, 2010, and assembled a control cohort of first-time mothers without JIA from the same administrative data, matching 4:1 for date of first birth, maternal age, and area of residence. We compared outcomes (stillbirth, prematurity, small for gestational age, and major congenital anomalies) in the JIA versus non-JIA groups using logistic regression.

Results. Mean age at delivery was 24.7 years in the JIA group (n = 1681) and 25.0 years for the non-JIA group (n = 6724). Women who had JIA were at higher risk for a premature baby [adjusted relative risk (RR) 1.20, 95% CI 1.01–1.42], a baby small for gestational age (adjusted RR 1.19, 95% CI 1.04–1.37), and a child with a congenital malformation (adjusted RR 6.51, 95% CI 5.05–8.39). Neural tube defects were higher in the JIA offspring: 1.61% (95% CI 1.11–2.33) versus 0.03% (95% CI 0.01–0.11) in the non-JIA group, as were congenital heart defects: 1.07% (95% CI 0.68–1.69) versus 0.58% (95% CI 0.42–0.79).

Conclusion. Most women with JIA will deliver a normal baby, even though they are at higher risk for having a child with adverse birth outcomes. Research is needed to understand pathophysiologic mechanisms and to investigate the effects of medications during childhood and youth on future birth outcomes. (J Rheumatol First Release February 1 2016; doi:10.3899/jrheum.150592)

Key Indexing Terms:
JUVENILE IDIOPATHIC ARTHRITIS CONGENITAL MALFORMATIONS COHORT STUDY

Juvenile idiopathic arthritis (JIA) is one of the most common chronic diseases of childhood, is often associated with severe joint destruction and disability, and frequently extends past adolescence into adulthood[1,2,3,4,5]. The incidence of JIA ranges between 10 and 20 per 100,000; its prevalence is estimated at 1 per 1000[6] and there is a female preponderance[7,8]. Management of JIA involves a multidisciplinary treatment approach including pharmacologic treatment, physical therapy, and occupational therapy[9]. Early intervention with disease-modifying antirheumatic drugs such as methotrexate (MTX) may help minimize joint damage[10,11] and achieve higher remission rates[12]. Many complications of the disease can potentially be avoided by early aggressive treatment[13,14]. Although mortality is low, longterm disability is a problem in 30% to 40% of patients[15].

An area that has received relatively little attention in JIA is that of pregnancy-related outcomes. The few studies that are available report on small samples. One retrospective study in Norway on 51 women with JIA described 76 pregnancy and fetal outcomes[16], and reported only 2 adverse outcomes: 1 infant with low birth weight and 1 stillbirth. A Polish study indicated that among 39 adult women, there were 23 who had at least 1 successful pregnancy; 7 had a spontaneous abortion or perinatal death of the child, 1 child developed JIA at age 3, and 1 other had a congenital heart defect[17]. In a study done in the United Kingdom on 246 adults with longstanding JIA, 30.5% of women had been pregnant[18]. Twenty-four percent of all pregnancies resulted in abortion, with 5.6% because of termination of pregnancy. These 3 studies were done on small groups and were descriptive, i.e., no comparison groups were included for analysis of associations between JIA and birth and pregnancy outcomes. One study in Australia used administrative data

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for women giving birth between 2000 and 2010; investigators identified 50 women who had been previously hospitalized for JIA and compared neonatal outcomes to those of the general population[19]. Findings indicated a higher risk of preterm birth (25.6% vs 6.6%), but no data on congenital anomalies were collected, and no data were available on persons with JIA who had not been previously hospitalized.

Given the paucity of data on this important issue, we aimed to determine whether women who had JIA in childhood and adolescence experienced more adverse neonatal outcomes than women who never had JIA. Specifically, we investigated neonatal outcomes such as stillbirth, prematurity, small for gestational age, all types of major congenital anomalies, and more particularly, congenital heart defects and neural tube defects.

MATERIALS AND METHODS

We designed a cohort study using administrative databases from the province of Quebec, Canada, which record information on provincially reimbursed physician services for all residents (including diagnosis and procedure codes) and all acute care hospitalizations (with up to 25 diagnostic codes and gestational age). We linked these sources to a third provincial database (Institute of Statistics of Quebec) that records demographic information on the mother and father as well as birth weight and gestational age for live births and stillbirths.

Physician claims in Quebec include an International Classification of Disease (ICD) diagnostic code. As a means of JIA case definition, we identified all women with at least 3 physician billing diagnostic ICD, 9th ed (ICD-9) codes of 714 who were ≤ 16 years of age at the time of the first billing code between January 1, 1983, and December 31, 2010, from the Quebec physician reimbursement and the hospitalization databases. ICD codes are limited in their ability to distinguish JIA from adult-onset rheumatoid arthritis (RA) because many physicians use the same code for both, but the approach of differentiating JIA from adult-onset RA by date of first 714 diagnostic billing code has been used by others[20,21]. Using the reimbursement and hospitalization databases, subjects meeting inclusion criteria were followed until December 31, 2010, to identify those who gave birth (stillbirth or live birth). These constituted the "exposed" JIA group, followed from the date of entry in the cohort (i.e., first billing diagnostic code of 714) until the time they gave birth for the first time between 1983 and 2010. Thus, only first births were included in our study. We also assembled a cohort of women from the same administrative databases who did not have these ICD physician billing diagnostic codes ≤ age 16, matched 4:1 for date of first birth (± 3 mos), age (± 5 yrs), and region of residence (using the first 3 digits of the postal code at the time of the birth) to serve as the "unexposed" non-JIA group. The beginning of pregnancy or the first day of gestation was defined as the first day of the last menstrual period (as reported in the hospitalization database). The end of pregnancy was the calendar date of the delivery. Start and end dates of pregnancy reported in these databases have been shown to be valid[22].

The following birth outcomes were identified: (1) stillbirth, defined as death prior to the complete expulsion or extraction from its mother of a product of conception (in Quebec, only stillbirths weighing ≥ 500 g must be reported, regardless of the gestation period); (2) prematurity, defined as < 37 weeks of gestational age; and (3) small for gestational age, defined as weight below the 10th percentile for gestational age as per Kramer, *et al*[23]. In addition, we determined major congenital anomalies and congenital heart defects diagnosed within the first 12 months of life to allow for delayed detections or registrations. The codes used to identify major congenital anomalies in the year following delivery were ICD-9: 740–759, excluding 743.6, 744.1, 744.2–744.4, 744.8, 744.9, 747.0, 747.5, 750.0, 752.4, 752.5, 754.6, 755.0, 755.1, 757.2–757.6, 757.8, 757.9, 758.4; and ICD, 10th ed: Q00–Q99, excluding Q08–Q10, Q162, Q17–Q19, Q250, Q270, Q381, Q515, Q516, Q20–Q53, Q664–Q666, Q689, Q70, Q81–Q84, Q94–Q95. All major congenital anomalies codes are physician-based and have been validated[24]. The data on stillbirth, gestational age, and birth weight have been validated using chart reviews as the gold standard[22]. The ICD-9 codes for major congenital anomalies in the administrative databases have been validated using mother's recall of the presence and type of malformations[24,25,26].

Data analyses were conducted as follows: first, we established the association between each of the neonatal outcome variables (i.e., stillbirth, prematurity, small for gestational age, major congenital malformations, congenital heart defects, and neural tube defects) and the JIA exposure status by using simple logistic regression. The strength of univariate associations was measured by relative risk (RR). Second, adjusted RR from multivariable logistic regression models were obtained, controlling for the following relevant variables: sex of the infant, residual differences in maternal age, maternal education (as a proxy for socioeconomic status), hypertension (HTN) and cardiovascular disease, and diabetes. This was done because maternal age is associated with neonatal outcomes[27,28], as are sex of the infant[29], HTN[30], cardiovascular disease[31], and diabetes[32], and though not a lot is known about these variables in mothers with JIA, there is some evidence that women who had JIA have higher rates of HTN[19] and lower socioeconomic status[33].

Among the JIA group, we also investigated (using bivariate analysis and logistic regression) whether having a visit to a rheumatologist (physician specialty was coded within the database) with a 714 diagnostic code in the 12 months prior to giving birth was associated with adverse birth outcomes. These women may have ongoing disease (symptoms in adulthood) and may be at higher risk for adverse birth outcomes similar to those with adult RA[34,35].

We received ethics approval for this study from the Commision d'accès à l'information du Québec (the Quebec commission for access to information) as well as the CERÈS (The Health Research Ethics Committee at the Université de Montréal).

RESULTS

The total number of births in Quebec between 1983 and 2010 was 2,357,494, and given the average fertility rate of 1.7, we calculate that the number of first births was 1,386,761 (total births divided by fertility rate). Our cohort consisted of 8405 women who experienced a first birth: 1681 women who had a history of JIA as a child or adolescent and 6724 women who never had JIA. For the entire cohort, the mean age at delivery was 24.9 years (SD 4.4) and the age range at delivery was 16 years to 46 years. There was a higher proportion of HTN among the JIA group (8.5%, 95% CI 7.3–9.9) than the non-JIA group (4.6%, 95% CI 4.2–5.2). Descriptive characteristics of the JIA and non-JIA groups are listed in Table 1.

There were more adverse neonatal outcomes in the JIA group (Table 2), with higher proportions of prematurity, small for gestational age, major congenital malformations, congenital heart defects, and neural tube defects. Among the JIA group, 485 persons (28.9%) had an adverse birth outcome (defined as at least 1 of the following: stillbirth, prematurity, small for gestational age, congenital malformation) compared with 1269 (18.9%) in the non-JIA group. In the JIA group, the proportion of congenital malformations was 9.0% (95% CI 7.8–10.5) versus 1.4% (95% CI 1.1–1.7) in the non-JIA group ($p < 0.001$). The proportion of neural tube defects was 1.6% (95% CI 1.1–2.3) in the JIA group versus 0.03% (95% CI 0.01–0.1) in the non-JIA group.

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Table 1. Characteristics of the cohort (n = 8405). Values are n (%) unless otherwise specified.

Characteristics	Exposed, JIA, n = 1681	Nonexposed, non-JIA, n = 6724	p
Age at delivery, yrs, mean (SD)	24.7 (4.3)	25.0 (4.5)	0.04
Age, yrs, median (range)	24.0 (16.0–40.0)	25.0 (16.0–46.0)	
Length of stay, days, mean (SD)	3.2 (1.8)	3.2 (2.2)	0.70
Length of stay, median (range)	3.0 (0.0–30.0)	3.0 (0.0–74.0)	
Female baby	849 (50.5)	3207 (47.7)	0.04
Lower level of education*	873 (51.9)	3424 (50.9)	0.46
HTN/heart disease**	143 (8.5)	311 (4.6)	< 0.001
Diabetes**	15 (0.9)	38 (0.6)	0.13

* Less than 14 years. ** Prior to or during pregnancy. JIA: juvenile idiopathic arthritis; HTN: hypertension.

We constructed individual multivariate logistic regression models for each neonatal outcome of interest except stillbirth (which had a low frequency in our cohort, and whose unadjusted RR and 95% CI were 2.29, 0.67–7.80). As for the other neonatal outcomes, the risks were substantially higher among women with a history of JIA for prematurity, small for gestational age, and major congenital malformations (Table 3). Especially striking were the results for major congenital malformations (adjusted RR 6.51, 95% CI 5.05–8.39), including congenital heart defects (adjusted RR 1.79, 95% CI 1.02–3.12). Covariates associated with adverse birth outcomes were lower maternal education for small for gestational age; HTN for prematurity, small for gestational age and congenital malformations; and older maternal age for congenital heart defects.

Table 2. Distribution of neonatal outcomes between exposed and nonexposed samples. Values are n unless otherwise specified.

Variables	Exposed, JIA, n = 1681	Nonexposed, non-JIA, n = 6724	p
Stillbirths, n (%)	4 (0.2)	7 (0.1)	0.18
Prematurity, n (%)	155 (9.2)	504 (7.5)	0.02
Small for gestational age, n (%)	235 (14.0)	776 (11.5)	0.006
Major congenital malformation, n (%)	152 (9.0)	92 (1.4)	< 0.001
Neurologic	30	3	
Eye, ear, face, neck	28	4	
Heart and circulatory	20	39	
Respiratory	1	1	
Digestive	7	5	
Genital	22	10	
Urinary	1	6	
Musculoskeletal	35	12	
Integument	0	0	
Chromosomal	2	5	
Other	6	7	
Congenital heart defect, n (%)	18 (1.1)	39 (0.6)	0.03
Neural tube defect, n (%)	27 (1.6)	2 (0.03)	< 0.001

JIA: juvenile idiopathic arthritis.

Among the JIA group, there were 107 (6.4%) who had a medical visit to a rheumatologist for ICD-9 code 714 within 1 year of giving birth and they had a higher frequency of major congenital malformations (Table 4). Logistic regression modeling, adjusting for covariates, indicated that having a medical visit with a rheumatologist for ICD-9 code 714 in the year preceding the birth was associated with having a child with a major congenital malformation (adjusted RR 2.15, 95% CI 1.41–3.28).

DISCUSSION

Our findings suggest that women with a history of JIA may be at increased risk for adverse neonatal outcomes, notably prematurity, small for gestational age, and major congenital malformation. However, it must be noted that most birth outcomes (71%) in mothers with JIA were favorable: i.e., not preterm, not small for gestational age, not stillborn, and free of major congenital anomalies.

To our knowledge, our large population-based study is the first to demonstrate the association between JIA and major congenital malformations. Our results differ from those of Chen, *et al*[19] who found that besides a higher risk for premature birth (adjusted OR 4.7, 95% CI 2.49–8.97), there were no other adverse neonatal outcomes among women who had a history of JIA. The authors stated that it was likely that the 50 JIA cases identified in their cohort of over 600,000 represented women with active and severe disease at the time of pregnancy and delivery, and at risk for worse pregnancy outcomes.

Chen, *et al*[19] did not report congenital malformations and assessed neonatal morbidity using a composite score that did not include malformations[36]. As mentioned, the number of women with JIA in their study was only 50 over the 10-year period (ours was 1681 over 28 yrs) and the study was likely underpowered. The method used was to identify JIA from hospital records and likely retrieved those who had more severe JIA (e.g., systemic onset); thus, patients with JIA who were not hospitalized could not be identified as having JIA in their study. Consequently, they may have had many more mothers with JIA who were not identified in that way, but were included in the comparison general population group, attenuating the results regarding neonatal morbidity.

We found an elevated risk of babies small for gestational age among women with JIA (RR of 1.19, 95% CI 1.04–1.37). In the study by Chen, *et al*[19], the adjusted OR was 1.05, but their 95% CI ranged between 0.5 and 2.2, possibly because of the small sample size of women with JIA. There was a higher frequency of children with congenital malformations born to women with JIA who had a visit to a rheumatologist for an ICD-9 code 714 within 12 months of giving birth, compared with those who did not have a visit within the year

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Table 3. Factors associated with adverse neonatal outcomes using logistic regression analyses. Values are adjusted relative risks (95% CI).

Variables	Prematurity*	Small for Gestational Age*	Congenital Malformations*	Congenital Heart Defects*
JIA	1.20 (1.01–1.42)	1.19 (1.04–1.37)	6.51 (5.05–8.39)	1.79 (1.02–3.12)
Maternal age, yrs**	1.02 (0.94–1.12)	0.99 (0.92–1.06)	1.14 (1.00–1.33)	1.42 (1.06–1.91)
Female baby	0.93 (0.80–1.08)	0.96 (0.86–1.08)	0.97 (0.76–1.23)	0.87 (0.52–1.46)
Education < 14 yrs	1.02 (0.87–1.20)	1.16 (1.02–1.32)	0.93 (0.71–1.21)	1.17 (0.67–2.06)
Hypertension/heart disease†	1.81 (1.42–2.30)	1.32 (1.06–1.65)	1.57 (1.06–2.30)	2.18 (0.99–4.81)
Diabetes‡	1.66 (0.83–3.31)	1.08 (0.54–2.16)	0.53 (0.08–3.60)	—

* Adjusted for all covariates in the model. ** Increment of 5 years. † Hypertension/heart disease prior to or during pregnancy. ‡ Diabetes prior to or during pregnancy. JIA: juvenile idiopathic arthritis.

Table 4. Birth outcomes in the JIA group among those with and without a visit to a rheumatologist for ICD-9 code 714 within 12 months of giving birth. Values are n (%) unless otherwise specified.

Variables	714 Visit, 12 Mos before Birth, n = 107	No 714 Visit, 12 Mos before Birth, n = 1574	p
Combined neonatal outcome*	43 (40.2)	442 (28.1)	0.008
Stillbirth	0 (0)	4 (0.3)	0.602
Prematurity	12 (11.2)	143 (9.1)	0.461
Small for gestational age	16 (15.0)	219 (13.9)	0.764
Major congenital malformation	21 (19.6)	131 (8.3)	< 0.001
Congenital heart defect	1 (0.9)	17 (1.1)	0.888
Neural tube defect	7 (6.5)	20 (1.3)	< 0.001

* Combined neonatal outcome is defined as having at least 1 adverse outcome. JIA: juvenile idiopathic arthritis; ICD-9: International Classification of Diseases, 9th ed.

before giving birth. These women may have ongoing symptoms and inflammation for which they sought medical advice. Prenatal inflammation[37] and certain medications taken during pregnancy[38,39] have both been associated with adverse outcomes. On the other hand, seeing a rheumatologist in the year prior to conception could also have resulted in counseling regarding medications, folic acid, etc. Because we do not know the actual severity of the disease among these people, our results must be interpreted with caution.

Our study did not examine medication use during either childhood/adolescence or pregnancy. To date, there have been no studies documenting associations between medications taken in childhood or adolescence and neonatal outcomes in women with JIA. However, based on evidence in the literature and expert opinions, it is recommended to avoid certain medications such as leflunomide and MTX during pregnancy, which are used for both RA and JIA[38,39].

Studies of women with RA have reported higher risk of premature births (OR 1.4–1.8)[34,35], babies small for gestational age (OR 1.2–1.6)[34,40], and congenital anomalies (OR 1.32)[35]. Although the risk for premature birth and small for gestational age are similar to our findings, the risk for congenital anomalies is substantially lower than what we found in our JIA cohort. However, a study suggested a 3-fold increased risk of congenital heart defects in children born to mothers with various systemic connective tissue disorders, including RA[41].

Potential biological mechanisms associated with adverse neonatal outcomes in JIA might include inflammation and/or imbalances in cell-mediated immunity and humoral immunity, which are associated with certain adverse neonatal outcomes[37,42,43]. A recent study reported that women who had adverse neonatal outcomes (specifically very and extremely low birth weight) were at higher risk of developing subsequent RA[44]. In that study, the diagnosis of RA occurred after the adverse neonatal outcome, but the implication is that there may be some common pathophysiologic process in rheumatic disease and adverse neonatal outcomes.

Adolescents with JIA may have nutritional deficiency [characterized by low body mass index (BMI)], which appears to occur not because of diet, but perhaps as a result of the disease process itself[45], which is the main exposure in our study. Further, low folate (a known risk factor for neural tube defects) could be a factor in women who had JIA among persons with JIA; some medications may increase the risk of adverse neonatal outcomes[46], such as MTX, which is a known teratogen (and also a folate antagonist). Although folate supplements are typically prescribed along with MTX, adherence to taking these are unknown. Longstanding effects of prolonged MTX use in youth and adolescence are also unknown.

The strengths of our study include the large sample size, a study period that incorporated data from 1983 to 2010, and the use of validated outcomes. A potential limitation is that

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there is no perfect case definition approach to JIA with ICD diagnostic codes. However, in our previously conducted data-based studies on juvenile RA (which is by far the largest subset of JIA), our incidence rates, mean age at diagnosis, and sex distribution statistics support the validity of our approach to case definition[47,48]. In our current study, we were even stricter in our definition of a case by including only those who had at least 3 coded visits (as opposed to at least 2 coded visits) as cases. Another potential limitation is that we did not have information on lifestyle factors such as diet and smoking in the administrative databases; however, these are associated with maternal education, which we did attempt to control for[49]. Further, adolescents with JIA may be less likely to smoke than those in the general population[50], making smoking less likely to explain our findings of the association between JIA and babies small for gestational age. We also did not have information on maternal BMI or alcohol consumption. A prospective study accounting for these confounders would be warranted.

Increased surveillance of mothers with JIA and their offspring might also explain some of our observed results; however, most of our outcomes (e.g., major congenital malformations, small for gestational age) are the type where incomplete ascertainment in controls seems unlikely. We were not able to distinguish between planned and spontaneous abortions and between types of preterm birth — spontaneous or induced, although both would be considered an adverse outcome. As mentioned earlier, we did not have information on medication use; however, we adjusted for having a rheumatology visit within the year prior to giving birth, which may be indicative of active disease and possible medication use. Admittedly, our results are based on a relatively small number of outcomes, although our dataset is the largest ever studied.

Our study suggested that mothers with a history of JIA may be at higher risk for premature births, small for gestational age births, and their offspring appear to be diagnosed more often with major congenital malformations. We do not know whether these differences are related to the effects of chronic disease or medications used for its treatment. Further research is needed to elucidate this issue, and should include studies to understand possible pathophysiologic mechanisms in JIA and pregnancy, as well as pharmacoepidemiologic studies to investigate the effects of medications during childhood and youth (including during the peripubescent period) on future neonatal outcomes. Although we did find elevated risk for adverse neonatal outcomes among mothers who had JIA, it must be noted that most babies born to mothers with JIA do not have adverse neonatal outcomes. Nonetheless, the implication is that women with a history of JIA who are pregnant should be monitored closely, and attention to folate levels is important. Our study will assist healthcare providers who are caring for pregnant (and pre-pregnant) women who have a history of JIA.

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