The final version of this paper was published in *Rheumatology* 2013; 52(6):1119-1125

Pregnancy outcomes in women with juvenile idiopathic arthritis: a population-based study

Jian Sheng Chen[1,2], Jane B. Ford[1], Christine L. Roberts [1], Judy M. Simpson[3], Lyn M. March[2]

1. Clinical and Population Perinatal Health Research, Kolling Institute of Medical Research, Sydney Medical School, University of Sydney, Sydney, Australia

2. Institute of Bone and Joint Research, Kolling Institute of Medical Research, Sydney Medical School, University of Sydney, Sydney, Australia

3. Sydney School of Public Health, University of Sydney, Sydney, Australia

Running title: Pregnancy and juvenile idiopathic arthritis

Address for correspondence:

Dr Jian Sheng CHEN,

Institute of Bone and Joint Research,

Level 4, Building 35, Royal North Shore Hospital, St Leonards 2065 NSW Australia

Tel: 61 2 9926 7348

Fax: 61 2 9906 1859

E-mail: jschen@med.usyd.edu.au

Key words: Juvenile idiopathic arthritis; Outcomes research; Pregnancy; Rheumatoid Arthritis

ABSTRACT

Objective: The aim of this study is to describe pregnancy outcomes among women with juvenile idiopathic arthritis (JIA).

Methods: Women who gave birth in New South Wales (NSW), Australia, were linked to hospital discharge records from 2000-2010. Women with an ICD-10-AM code of M08 or M09 in the hospital records were considered to have JIA. Logistic regression was used to calculate odds ratios for pregnancy outcomes and the lack of independence in study outcomes for multiple pregnancies in the same woman was taken into account using generalised estimating equations.

Results: During the study period, 601,659 women had 941,496 births. Of these births, 78 births could be attributed to 50 women with JIA. Of the 78 JIA pregnancies, 53 (68%) were delivered by either CS (n=40, 51%) or instrumental delivery (n=13, 17%); and compared to the other women, those with JIA had significantly higher rates of preeclampsia, postpartum haemorrhage and severe maternal morbidity. Compared to other infants, those with mothers with JIA were more likely to be born premature but were not at increased risk of being small for gestational age, requiring neonatal intensive care, low Apgar score at 5 minutes or severe neonatal morbidity.

Conclusions: Infants of women with JIA did not have an increased risk of adverse neonatal outcomes. Intensive obstetric care might be required during pregnancy for women with JIA given the increased risk of maternal morbidity..

Key messages:

Women with JIA are at increased risk of maternal complications.

Risk of adverse neonatal outcomes is not increased except preterm birth.

Medical advice and intensive obstetric care should be provided.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is a chronic inflammatory disease of the joints and extra-articular tissue, and can lead to long-term damage of the affected areas. About 10% to 20% of adults with juvenile-onset arthritis have moderate to severe functional limitations [1]. Many adults with a history of JIA also have a poor self image of their body, exhibit anxiety and depression, and report reduced social activity [1,2]. The overall prevalence of juvenile-onset arthritis in women of childbearing age is estimated to be about 1 to 2 per 1,000 women [1,3]. Physical impairments and the associated psychological aspects of JIA will have impacts on all aspects of life including women's reproduction. Compared to their healthy counterparts, women with a history of JIA have similar desire to have children but are more reluctant to become pregnant and the cited reasons include functional impairment, fear of transmitting JIA to their offspring and physician's advice [4,5].

Several studies have investigated the impacts of JIA on women's reproduction and the results are mainly based on self-reported information (questionnaire) with contradictory findings [2,5-7]. In a recent study of 75 Norwegian women with JIA, only 43% (n=32) had a history of pregnancy compared to the rate of 59% in the general population, a 16% reduction in pregnancy rate [7].

Some studies also reported an increased rate of miscarriages or abortions in women with JIA [5]. In contrast, other studies observed similar rates of live birth and miscarriages in women with JIA [6]. With the exception of a reported increase in risk of caesarean section (CS) [4], there is almost no information on neonatal and maternal outcomes of pregnancies among women with JIA.

This study describes pregnancy outcomes among women with a history of JIA and compares their outcomes with the general population using population health data. Understanding the consequences should provide important insights into target areas for health care providers and for counselling women with JIA who are prepared to or have already become pregnant about what to expect for their birth.

METHODS

Data sources and study population

Two population health datasets were used: the New South Wales (NSW) Perinatal Data Collection ('birth data') and the NSW Admitted Patient Data Collection ('hospital data'). The birth data include all live births or stillbirths of at least 20 weeks gestation or at least 400 grams birth weight in NSW. Information collected in the birth data includes demographics, number of previous births and maternal health, pregnancy, labour, delivery, and perinatal outcomes. The hospital data covers every inpatient admission in NSW, and includes demographic and episode-related data. Data from the medical records are coded according to the tenth revision of the International Classification of Diseases Australian Modification (ICD-10-AM) and the affiliated Australian Classification of Health Interventions [8]. Record linkage of birth data and hospital

data (both mother and baby) by the Centre for Health Record Linkage [9] was approved by the NSW Population and Health Services Research Ethics Committee. Only de-identified data were made available to researchers.

Women in the birth dataset were linked to their medical records in the hospital data from July 1, 2000 to December 31, 2010. Women with an ICD-10-AM code of M08 or M09 in any hospital record in the linked dataset were considered as having had juvenile-onset arthritis and were compared to other women giving birth during the study period. A diagnosis could be recorded in antenatal, birth and postpartum hospital records as well as records prior to pregnancy for women who gave birth during the study period. Up to 20 diagnoses and 20 procedures in each record were used for disease identification in this study.

Ascertainment of risk factors and study outcomes

Variables ascertained from birth data and/or hospital data included maternal age, maternal hypertension (gestational, preeclampsia or chronic), maternal diabetes (gestational or pre-gestational), smoking during pregnancy, socio-economic status based on residential postcode (Index of Relative Socio-economic Disadvantage [10]), inter-pregnancy interval (interval between first and second births minus gestational age of the second birth), number of births, any abortion or miscarriage (including those before 20 weeks gestation), preterm birth (<37 weeks gestation), infants small for gestational age (birth weight<10^{th} percentile for age and sex [11]), Apgar score at 5 minutes (<7), admission to neonatal intensive care unit (NICU >4 hours), severe neonatal morbidity (a composite indicator for measuring severe adverse neonatal outcomes [12]), CS, labour induction, episiotomy, instrumental delivery, antepartum haemorrhage (including

placental abruption), preeclampsia, postpartum haemorrhage, severe maternal morbidity (a composite indicator for measuring major maternal morbidity [13]), severe perineal trauma (3^{rd}-4^{th} degree tear) and length of hospital stay for mother.

Data analysis

Differences between women with and without JIA in age at first birth, abortion rate, length of hospital stay, the first and second pregnancy interval, number of births, proportion of women with more than one birth etc were compared using the chi-square test, ANOVA test or Wilcoxon rank-sum test where appropriate. Logistic regression analysis was used to calculate odds ratios (OR) for each pregnancy outcome for women with JIA compared with the rest of the birthing population; the lack of independence in study outcomes for multiple pregnancies in the same woman was taken into account using generalised estimating equations (GEE). The analyses were performed with and without adjusting for known determinants of pregnancy outcomes.

RESULTS

During the study period, 601,659 women had 941,496 births. Of these, 78 births could be attributed to 50 women who had a diagnosis code of juvenile arthritis in the hospital data. Based on the last birth record, the average number of births was 1.8 for women with JIA and 2.2 for the wider birthing population (Table 1). The frequency distribution of pregnancies for the women with and without JIA is shown in Figure 1. There were 19 women with JIA who had both first and second birth records in this dataset.

Median age at first birth was similar for women with JIA and the rest of the birthing population (P=0.07)(Table 1). For women with JIA, maternal age for any birth ranged from 16.4 to 42.3 years. Of these 50 women, 6 (12%) had an abortion or miscarriage during the study period; this rate was not different from the 16% observed in the wider birthing population (P=0.48). With respect to fertility after the first birth, a significantly smaller proportion of women with JIA (48%) had more than one birth than in the wider birthing population (68%, P=0.003). However, among those who did have more than one birth, there was no difference in first to second pregnancy interval between the two groups (Table 1, P=0.67 for median).

Of the 78 JIA pregnancies, 53 (68%) were delivered by either CS (n=40, 51%) or instrumental delivery (n=13, 17%). Among the 40 CS, 31 (78%) were prelabour deliveries. Compared to the wider birthing population, women with JIA had significantly higher rates of preeclampsia, postpartum haemorrhage and severe maternal morbidity; and their pregnancies were significantly more likely to be delivered by CS or instrumentally even after adjusting for potential confounders including socio-economic status (see footnotes of Table 2). Length of stay for the birth admission was longer in women with JIA than in the wider birthing population (mean: 7.1 vs 4.0 days and median: 5 vs 4 days for women with JIA and the general population respectively; P<0.001 for median). However, no differences between the two groups were observed in the other maternal outcomes: induction of labour, use of epidural, antepartum haemorrhage, episiotomy and 3^{rd}-4^{th} degree tear.

Compared to infants from the wider birthing population, infants from women with JIA were more likely to be born preterm and to be admitted to a NICU and had a higher rate of severe neonatal morbidity (Table 3). After adjusting for the predictors maternal age at birth, nulliparity,

hypertension, diabetes, socio-economic status and smoking during pregnancy, preterm birth remained statistically significantly different between the two groups. The differences in rates of severe neonatal morbidity and admission to a NICU disappeared after adjusting for these predictors and preterm birth. There was no difference in rates of infants small for gestational age or Apgar score < 7 at 5 minutes between the two groups.

DISCUSSION

To our knowledge, this is the first study that specifically investigates relationships between juvenile idiopathic arthritis and pregnancy outcomes. The results indicate that women with a history of JIA are at increased risk of preterm delivery, obstetric interventions (CS or instrumental delivery) and the maternal complications preeclampsia, postpartum haemorrhage and severe maternal morbidity. Also, compared to the wider birthing population, women with JIA had a longer birth admission and were less likely to become pregnant again. However, the rate of abortion or miscarriage and the inter-pregnancy interval were similar among all women with a history of birth regardless of their JIA status. Importantly, after controlling for the impact of known determinants of neonatal outcomes, there were no differences between women with JIA and their healthy counterparts in neonatal outcomes except that the rate of preterm birth was higher in women with JIA.

For maternal outcomes, other studies of women with rheumatoid arthritis also reported an elevated risk of preeclampsia [14,15]. In contrast, in their study of first births, Wallenius et al [16] found that, compared to the general population, 128 women with chronic inflammatory arthritis (including JIA) were not at increased risk of preeclampsia, instrumental delivery or

postpartum haemorrhage but were at risk of vaginal bleeding during pregnancy, CS and induction of labour. The reason for the increased risk of preeclampsia in our study is unclear and may be related to use of corticosteroids during the pregnancy [17]. Unfortunately, our datasets did not include information on use of drugs so we could not explore this possibility. The increased risk of postpartum haemorrhage in our study was not related to the high CS rate in cases as the size of the risk did not change with additional adjustment for CS in the regression model (data not shown). One explanation could be use of non-steroidal anti-inflammatory drugs (NSAIDs) during the pregnancy among the JIA patients. Women might use NSAIDs while they were pregnant despite labels that warn against doing so. In a USA case-control study published in 2001, 25% of the meconium samples in the control group were positive for NSAIDs [18]. NSAIDs inhibit prostaglandin synthesis and may lead to increased blood loss during the postpartum period as prostaglandins are potent vasodilators and increase the permeability of blood vessels [19]. NSAIDs also have an anti-platelet effect and can increase bleeding through that mechanism [20].

In women with a history of JIA, the high probability of an obstetric intervention during pregnancy is notable. In our study, two thirds of JIA pregnancies involved either CS (51%) or instrumental delivery (17%). Over 20 years ago, the high CS rate among women with JIA was already reported by Ostensen et al [4] and in that study, 24 of 76 (32%) JIA pregnancies were delivered by CS and, of these 24, 15 (63%) were due to sequelae of JIA. Several studies on women with rheumatoid arthritis also reported increased risk of CS [14,15,21]. However, the finding of increased risk of instrumental delivery in women with JIA in our study has not been reported previously. The observed increased risk of obstetric interventions in women with JIA

could be a result of their physical impairments. Physical impairments such as chronic or recurrent pain or discomfort, incomplete use of feet or legs etc, are more pronounced in women with JIA than in women with adult-onset arthritis [1]. The high rate of maternal morbidity is also of concern. Intensive obstetric care should therefore be provided during antenatal, birth and postpartum periods for women with JIA.

For women with JIA who are planning to have children, the results of neonatal outcomes in our study might provide some comfort; but they should be aware the study is based on a small number of women with JIA. Although only a small number of women with JIA were included in the study, they were likely to be severe cases as they were identified from hospital records. Hospital data only record diseases or conditions that require hospitalisation or that affect a hospital admission. Other studies also found that risks of birth defect and transfer to NICU were not increased in women with chronic inflammatory arthritis [16,21,22]. However, increased risk of any or spontaneous preterm birth was found in our study and in other studies of women with chronic inflammatory arthritis [16,21,22]. Iatrogenic preterm birth might be a result of a timely delivery, albeit prematurely, to avoid stillbirth or complications. In the 1980s and 1990s, women with autoimmune rheumatic diseases were often advised to avoid pregnancy [4]. It is now known that avoiding pregnancy when the diseases are active and continuing to take appropriate medication to keep autoimmune disease suppressed during pregnancy can reduce the risk of adverse pregnancy outcomes [17]. In a recent study, Viktil et al reported that the risk of congenital malformations was not increased in children born to mothers or fathers who had received anti-rheumatic drugs 3 months prior to pregnancy and/or during pregnancy [23]. Co-

operation between obstetricians and physicians in caring for women with JIA could provide satisfactory pregnancy outcomes.

With respect to women's reproduction and fetal loss, contradictory findings to ours were reported in a case-control study by Ostensen et al in 2000 [5]. The authors found that Norwegian women with JIA (n=126) had a reduced fecundity and an increased risk of miscarriage but their fertility was not impaired. In another study of 176 women with JIA who had mean disease duration of 28 years in United Kingdom in 2002, Packham et al reported women with psoriatic JIA had a significantly higher incidence of miscarriage (33%) than the other JIA groups (11%) [2]. In contrast, in two JIA case-control studies, Peterson et al [6] (44 cases) reported similar pregnancy rate and childbirth rate between two study groups in United States in 1997 and Wallenius et al [7] (75 cases) reported similar median inter-pregnancy interval among all study women in Norway in 2011. Inconsistent results from these studies may be attributed to the small number of JIA cases in each study and/or differences in study methodology, study period and patient selection.

A major limitation of our study is under ascertainment of JIA cases from hospital records. Only 50 women were identified from 601,659 women who gave birth over 10.5 years in NSW representing probably less than 10% of the JIA cases. However, they would represent a much higher proportion of those women with active disease during the study period. Many children with arthritis will outgrow their illness and overall the prognosis of JIA is favourable, although this is dependent on the disease type [24]. For example, about 50% of systemic onset JIA cases remit without recurrence in adult. Our study patients would presumably be among those with the

most active disease and so might be expected to have the worst pregnancy outcomes. Using all other women who gave birth during the study period as the reference group in our study, a negative result for women with JIA could be reassuring. Other limitations of our study include not knowing the type of JIA, the nature or degree of the women's joint involvement and physical impairments, disease recurrence or use of medications. It is possible that we have underestimated pregnancy losses, with only those resulting in hospital presentation included in our data. Similar rates of pregnancy loss across the study population suggest ascertainment is not higher in women with JIA. With only 6 cases of pregnancy loss in women with JIA it is hard to draw strong conclusions.

In summary, women with a history of JIA in our study did not have an increased risk of having infants with adverse neonatal outcomes but premature birth could be a concern. Also, CS or instrumental delivery was often required which could be due in part to their physical impairment so it is recommended that intensive obstetric care be provided during pregnancy. Women with JIA might experience more maternal complications due to use of medications to suppress the disease activity or to the disease itself. Co-operation between obstetricians and family physicians at the pregnancy planning stage and during the pregnancy should reduce these risks.

ACKNOWLEDGEMENTS

The authors thank the NSW Department of Health for access to the population health data and the NSW Centre for Health Record Linkage for linking the data sets.

Funding statement: This work was supported by an Australian National Health and Medical Research Council (NHMRC) Capacity Building Grant (#573122).

Conflict of interest statement: The authors declare no conflicts of interest.

REFERENCES

1 Australian Institute of Health and Welfare. Juvenile arthritis in Australia. 2008; Arthritis series no. 7. Cat. no. PHE 101. Canberra: AIHW.

2 Packham JC , Hall MA. Long-term follow-up of 246 adults with juvenile idiopathic arthritis: social function, relationships and sexual activity. Rheumatology (Oxford) 2002; 41: 1440-1443.

3 Borchers AT, Selmi C, Cheema G et al. Juvenile idiopathic arthritis. Autoimmun Rev 2006; 5: 279-98.

4 Ostensen M. Pregnancy in patients with a history of juvenile rheumatoid arthritis. Arthritis Rheum 1991; 34: 881-87.

5 Ostensen M, Almberg K, Koksvik HS. Sex, reproduction, and gynecological disease in young adults with a history of juvenile chronic arthritis. J Rheumatol 2000; 27: 1783-87.

6 Peterson LS, Mason T, Nelson AM et al. Psychosocial outcomes and health status of adults who have had juvenile rheumatoid arthritis: a controlled, population-based study. Arthritis Rheum 1997; 40: 2235-40.

7 Wallenius M, Skomsvoll JF, Irgens LM et al. Fertility in women with chronic inflammatory arthritides. Rheumatology (Oxford) 2011; 50: 1162-67.

8 National Centre for Classification in Health. Australian Coding standards for ICD-10-AM and ACHI. 2004; 5th: 202.

9 Lawrence G, Dinh I, Taylor L. The Centre for Health Record Linkage: a new resource for health services research and evaluation. HIM J 2008; 37: 60-62.

10 Australian Bureau of Statistics. Information Paper: An Introduction to Socio-Economic Indexes for Areas (SEIFA). 2006. Accessed date: 18/05/2012. http://www.abs.gov.au/ausstats/abs@.nsf/mf/2039.0

11 Roberts CL , Lancaster PA. Australian national birthweight percentiles by gestational age. Med J Aust 1999; 170: 114-18.

12 Lain SJ, Algert CS, Nassar N et al. Incidence of severe adverse neonatal outcomes: use of a composite indicator in a population cohort. Matern Child Health J 2012; 16: 600-608.

13 Roberts CL, Cameron CA, Bell JC et al. Measuring maternal morbidity in routinely collected health data: development and validation of a maternal morbidity outcome indicator. Med Care 2008; 46: 786-94.

14 Lin HC, Chen SF, Lin HC et al. Increased risk of adverse pregnancy outcomes in women with rheumatoid arthritis: a nationwide population-based study. Ann Rheum Dis 2010; 69: 715-17.

15 Skomsvoll JF, Ostensen M, Irgens LM et al. Pregnancy complications and delivery practice in women with connective tissue disease and inflammatory rheumatic disease in Norway. Acta Obstet Gynecol Scand 2000; 79: 490-495.

16 Wallenius M, Skomsvoll JF, Irgens LM et al. Pregnancy and delivery in women with chronic inflammatory arthritides with a specific focus on first birth. Arthritis Rheum 2011; 63: 1534-42.

17 Gordon C. Pregnancy and autoimmune diseases. Best Pract Res Clin Rheumatol 2004; 18: 359-79.

18. Alano MA, Ngougmna E, Ostrea EM et al. Analysis of nonsteroidal antiinflammatory drugs in meconium and its relation to persistent pulmonary hypertension of the newborn. Pediatrics 2001; 107: 519-23.

19 Fiddler MA. Rheumatoid arthritis and pregnancy: issues for consideration in clinical management. Arthritis Care Res 1997; 10: 264-72.

20 Gladding PA, Webster MW, Farrell HB et al. The antiplatelet effect of six non-steroidal anti-inflammatory drugs and their pharmacodynamic interaction with aspirin in healthy volunteers. Am J Cardiol 2008; 101: 1060-1063.

21 Reed SD, Vollan TA, Svec MA. Pregnancy outcomes in women with rheumatoid arthritis in Washington State. Matern Child Health J 2006; 10: 361-66.

22 Norgaard M, Larsson H, Pedersen L et al. Rheumatoid arthritis and birth outcomes: a Danish and Swedish nationwide prevalence study. J Intern Med 2010; 268: 329-37.

23 Viktil KK, Engeland A, Furu K. Outcomes after anti-rheumatic drug use before and during pregnancy: a cohort study among 150,000 pregnant women and expectant fathers. Scand J Rheumatol 2012; 41: 196-201.

24 Minden K, Kiessling U, Listing J et al. Prognosis of patients with juvenile chronic arthritis and juvenile spondyloarthropathy. J Rheumatol 2000; 27: 2256-63.

Table 1 Characteristics at birth for women who gave birth in NSW during July 1, 2000 to December 31, 2010

Characteristics at birth	Women with Juvenile idiopathic arthritis N=78 births to 50 women	General women N=941,496 births to 601,659 women	P* value
Maternal age at any birth (year),^ median (range)	29.5 (16.4 to 42.3)	30.6 (12.1 to 56.2)	0.09
Nullipara at any birth,^ n (%)	44 (56)	394,569 (42)	0.01
Plurality at any birth,^ n (%)	2 (2.6)	14,784 (1.6)	0.48
Hypertension at any birth,^ n (%)	12 (15)	86,693 (9.2)	0.06
Diabetes at any birth,^ n (%)	6 (7.7)	56,435 (6.0)	0.53
Smoking during pregnancy at any birth,^ n (%)	10 (13)	132,148 (14)	0.76
Socio-economic status # at any birth,^ n (%)			0.82
Most disadvantaged	14 (18)	204,720 (22)	
Disadvantaged	14 (18)	177,659 (19)	
Average	18 (23)	187,026 (20)	
Advantaged	12 (15)	180,076 (19)	
Most advantaged	20 (26)	182,215 (20)	
Maternal age at first birth (year), median (range)	28.1 (16.4 to 40.3)	28.9 (12.1 to 56.2)	0.07
Abortion/miscarriage during the study period, n (%)	6 (12)	94,107 (16)	0.48
Nullipara at last birth, n (%)	26 (52)	194,345 (32)	0.003
Number of births at last birth, mean (SD)	1.8 (1.0)	2.2 (1.2)	0.02
Interval between 1st and 2nd pregnancies (years), median (range)	2.1 (1.5 to 3.5)	2.3 (0.8 to 10.5)	0.67

^ Based on all 941,496 births during July 1, 2000 to December 31, 2010
* Chi-square test, ANOVA test or Wilcoxon rank-sum test where appropriate
# Using Index of Relative Socio-economic Disadvantage for Areas

Table 2 Odds ratios (ORs)* of maternal outcomes for women with juvenile idiopathic arthritis

Outcome variable	Risk factor		%	Unadjusted OR [95%CI]	Adjusted! OR [95%CI]
Caesarean section					
	Juvenile RA	Yes	51.3	2.59 [1.54, 4.38]	2.78 [1.65, 4.68]
		No	27.7	1.00	1.00
Elective caesarean section					
	Juvenile RA	Yes	39.7	3.58 [2.11, 6.08]	4.64 [2.64, 8.15]
		No	15.8	1.00	1.00
Induction of labour					
	Juvenile RA	Yes	21.8	0.84 [0.48, 1.49]	0.73 [0.39, 1.36]
		No	25.2	1.00	1.00
Epidural					
	Juvenile RA	Yes	34.6	1.39[0.81, 2.38]	1.24 [0.68, 2.27]
		No	25.4	1.00	1.00
Episiotomy^					
	Juvenile RA	Yes	13.2	0.78 [0.31, 1.98]	0.69 [0.26, 1.82]
		No	15.9	1.00	1.00
Instrumental delivery^					
	Juvenile RA	Yes	34.2	2.99 [1.52, 5.90]	3.00 [1.34, 6.71]
		No	14.7	1.00	1.00
3^{rd}-4^{th} degree tear^					
	Juvenile RA	Yes	0	N/A	N/A
		No	2.5	1.00	1.00
Preeclampsia					
	Juvenile RA	Yes	7.7	3.10 [1.36, 7.03]	2.80 [1.23, 6.38]
		No	2.6	1.00	1.00
Antepartum haemorrhage					
	Juvenile RA	Yes	1.3	0.97 [0.13, 7.08]	0.95 [0.13, 7.00]
		No	1.4	1.00	1.00
Postpartum haemorrhage					
	Juvenile RA	Yes	18.0	2.45 [1.27, 4.72]	2.35 [1.23, 4.50]
		No	8.3	1.00	1.00
Severe maternal morbidity					
	Juvenile RA	Yes	7.7	5.52 [1.81, 16.9]	5.11 [1.70, 15.3]
		No	1.4	1.00	1.00

* Lack of independence in study outcomes for multiple pregnancies in the same woman was taken into account using generalised estimating equations (GEE).
! Adjusted for maternal age (i.e. <20, 20-34 and ≥35 years), parity, hypertension (except preeclampsia model), diabetes, socio-economic status and smoking during pregnancy.
^ Excludes CS births.

Table 3 Odds ratios (ORs)* of neonatal outcomes for women with juvenile idiopathic arthritis

Outcome variable	Risk factor		%	Unadjusted OR [95%CI]	Adjusted! OR [95%CI]
Preterm birth (<37 weeks)					
	Juvenile RA	Yes	25.6	4.99 [2.71, 9.20]	4.72 [2.49, 8.97]
		No	6.6	1.00	1.00
Spontaneous preterm birth (<37 weeks)^					
	Juvenile RA	Yes	13.4	2.99 [1.23, 7.28]	2.89 [1.16, 7.24]
		No	5.0	1.00	1.00
Small for gestational age (<10th percentiles)					
	Juvenile RA	Yes	10.3	1.18 [0.56, 2.47]	1.05 [0.50, 2.21]
		No	9.5	1.00	1.00
Severe neonatal morbidity					
	Juvenile RA	Yes	11.5	3.03 [1.55, 5.95]	1.12 [0.50, 2.49]
		No	4.2	1.00	1.00
Apgar score at 5 minutes (<7)					
	Juvenile RA	Yes	2.6	1.88 [0.47, 7.52]	1.04 [0.28, 3.85]
		No	1.4	1.00	1.00
Admission to neonatal intensive care unit (>4 hrs)					
	Juvenile RA	Yes	33.3	2.74 [1.56, 4.83]	1.56 [0.87, 2.81]
		No	15.4	1.00	1.00

* Lack of independence in study outcomes for multiple pregnancies in the same woman was taken into account using generalised estimating equations (GEE).

! Adjusted for maternal age (i.e. <20, 20-34 and ≥35 years), parity, hypertension, diabetes, socio-economic status and smoking during pregnancy. Additional adjustment for preterm birth was applied to severe neonatal morbidity, Apgar score at 5 minutes and admission to neonatal intensive care unit.

^ Excludes planned births, i.e. occurred before labour.

Figure 1 Frequency distribution of pregnancies by status of juvenile idiopathic arthritis