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Original Article

Clinical science

A population-based study of caesarean section in women with juvenile idiopathic arthritis

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Abstract

Objectives: The literature on delivery methods in women with JIA is limited. Active inflammation is a risk factor for caesarean section (CS) in other arthritic diseases. A CS entails a higher risk for complications than vaginal delivery and restricted physical activity in the first weeks after birth. Our objective was to explore a possible association of inflammatory active disease and the proportion of CS in women with JIA.

Methods: Data from the Norwegian nationwide observational register RevNatus were linked with data from the Medical Birth Registry of Norway (MBRN). Cases comprised singleton births in women with JIA ($n = 196$) included in RevNatus from 2010 to 2019. Singleton births registered in the MBRN during the same period of time, excluding births in mothers with rheumatic inflammatory diseases, served as population controls ($n = 575\,798$).

Results: CS was more frequent in women with JIA (20.4%) and in the subgroup of women with inflammatory active JIA (30.0%) than in population controls (15.6%). Women with active JIA had a risk for elective CS similar to population controls [risk difference 2.3% (95% CI −2.5, 12.9)] and a higher risk for emergency CS [risk difference 14.0% (95% CI 4.3, 27.4)] compared with population controls.

Conclusion: Women with active JIA had a higher risk for emergency CS, but not elective CS, compared with population controls.

Lay Summary

What does this mean for patients?

Vaginal birth is the preferred choice of delivery. However, a caesarean section (CS) may be a necessary intervention to prevent potential harm to the mother or baby. The reasons for considering a CS include underlying risk factors of the mother, earlier births and psychosocial factors. In women with JIA, active disease, joint damage, medication and health-related quality of life may be additional factors. We compared CS in women with JIA and healthy controls to see if it was more frequent in women with JIA. We found that CS overall was more frequent in women with active JIA than in healthy controls, but was not increased in women with inactive JIA. Women with active JIA had a higher risk for emergency CS compared with healthy controls. The risk for elective CS in women with active JIA was similar to that of healthy controls. Women with JIA who are planning pregnancy or are pregnant are advised to contact their rheumatologist for tighter follow-up, with a goal of well-controlled disease during pregnancy.

Keywords: pregnancy and rheumatic disease, JIA, epidemiology, inflammation

Key messages

- Caesarean section was more frequent in women with active JIA than in population controls.
- Women with active JIA had a higher risk for emergency CS compared with population controls.
- The results call for tight monitoring targeting inactive disease before and throughout pregnancy.

Introduction

JIA is a heterogeneous group of arthritic diseases with onset before 16 years of age [1]. It is the most common chronic rheumatic disease in childhood, affecting twice as many girls as boys. An incidence of 15/100 000 children per year has been reported in the Nordic countries. The median age of onset is 6.8 years, with an early peak of incidence at <3 years in girls [2]. A follow-up study in early adulthood (18 years

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after onset) reported active disease in 53%, on or off medication [3].

The rate of caesarean section (CS) has gradually increased over the last 30 years and is performed in one of five deliveries worldwide [4]. Among the developed countries, the Nordic countries have the lowest rates, at ≈17% in 2014 [5]. A CS may be a crucial intervention for mother and child. Due to potential negative short- and long-term health effects, it should only be performed when indicated according to obstetric evidence-based practice [6].

Recent prospective studies have reported CS to be more frequent in populations of women with inflammatory joint diseases [7], as well as in women with JIA [8–10], compared with healthy controls. International guidelines advocate planning pregnancy in women with rheumatic diseases, targeting well-controlled disease on medication compatible with pregnancy at least 6 months before conception [11]. This has resulted in better outcomes in recent decades. Withdrawal of teratogenics like MTX without initiating medication compatible with pregnancy, undue cessation of medication compatible with pregnancy due to fear of harming the foetus or unplanned pregnancy may still result in active disease during pregnancy.

The reason for considering CS may be a combination of factors, including underlying maternal risk factors, earlier obstetric history and psychosocial factors. In women with JIA disease activity, joint damage, medication and health-related quality of life (HRQoL) may add to this complexity.

To the best of our knowledge, CS in women with JIA has not yet been investigated using available disease activity assessments during pregnancy. We aimed to explore a possible association between inflammatory active JIA and the occurrence of CS, overall as well as for elective and emergency CS.

Patients and methods

Study population

Data from RevNatus was linked with data from the Medical Birth Registry of Norway (MBRN) in this population-based cohort. RevNatus is a Norwegian nationwide medical quality register that includes women with inflammatory rheumatic diseases. It has prospective follow-up from the time of planning a pregnancy until 1 year after delivery. Patients >16 years of age with a rheumatic diagnosis planning pregnancy or who are pregnant are eligible for inclusion. RevNatus is operated by the Norwegian National Advisory Unit on Pregnancy and Rheumatic Diseases (NKSR). National guidelines disseminated by the NKSR recommend that all women of childbearing age diagnosed with an inflammatory rheumatic disease should be informed about the importance of planning pregnancy. Patients are advised to contact their rheumatology unit when they have a pregnancy wish, or when pregnant, for closer follow-up. The local outpatient rheumatology clinics include eligible women in RevNatus and follow the patient preconception, in every trimester of the pregnancy and 6 weeks and 6 and 12 months after delivery. Demographic variables, disease activity assessment, medication, laboratory status, pregnancy outcome, self-reported health status and breastfeeding are recorded.

The MBRN is a mandatory national health registry. Information about maternal health before and during pregnancy are registered in a personal maternity record during routine antenatal care appointments, starting in the first trimester. Maternal and neonatal complications are registered after delivery. The maternity units are responsible for electronic notification to the MBRN of all collected data within 1 month after birth. Data are available for research purposes ≈2 years after registration. Maternal inflammatory rheumatic diseases have been coded in the MBRN according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) since December 1998 [12].

Singleton births recorded in the MBRN from 2010 to 2019 were eligible for inclusion in the present study. Births among women with a diagnosis of JIA recorded in the MBRN (ICD codes M08.0, M08.1, M08.2, M08.3, M08.4, M08.8 and M08.9) that were also recorded in RevNatus as JIA formed the total JIA cohort. The population controls were the remaining births recorded in the MBRN, after excluding births in women with other inflammatory rheumatic diseases.

The total JIA cohort was grouped into births in women with inactive and women with active JIA according to registered disease activity scores in second or third trimester. The main outcomes were CS, elective CS and emergency CS in population controls, total JIA cohort, inactive JIA group and active JIA group. Maternal factors relevant for the main outcomes were reported and compared between population controls and the total JIA cohort. Disease-related factors including medications and HRQoL parameters were reported for the total JIA cohort and the disease activity groups and compared between women with inactive and active JIA.

Ethics

Written informed consent is required before inclusion in RevNatus. The registry was approved by the Regional Committee for Medical and Health Research Ethics (REK) Mid Norway in 2006. The present study was approved by REK Mid Norway in June 2019 (2019/779/REK Midt) and July 2020 (minor change). Access to data from the MBRN was granted in June 2020 (MBRN assignment PDB 2804).

Variables

Patient group variables comprised educational status, disease-specific information including disease activity and medication, and self-reported health status and were retrieved from RevNatus. Maternal variables including age, parity, smoking, BMI, diabetes, assisted reproductive technology (ART), previous CS and mode of delivery in the current pregnancy were derived from the MBRN.

Disease activity assessment

The Juvenile Arthritis Disease Activity Score (JADAS) is not validated for use in adults with JIA. Disease activity was therefore assessed using the three-variable 28-joint DAS with CRP (DAS28-CRP-3), a composite score used in RA and other arthritic diseases and validated for use in pregnant women with RA [13]. It consists of the number of tender and swollen joints among 28 joints and CRP [14]. The EULAR has defined four disease categories, with scores ranging from 0 to 10: remission (<2.6), low disease activity (≥2.6–≤3.2), moderate disease activity (>3.2–≤5.1) and high disease activity (>5.1) [15]. We defined inactive JIA as DAS28-CRP-3 <2.6 and active JIA as DAS28-CRP-3 ≥2.6.

HRQoL

The 36-item RAND Health Survey (RAND-36) [16] is a composite measure of different aspects of HRQoL. The RAND-12

[17] is a modification using a subset of 12 items from the RAND-36. The two questionnaires cover eight domains scored 0–100. A higher score indicates a higher HRQoL. A change or difference in score >5 points is considered a minimal clinically important difference (MCID), with ≥5–<10 considered a marginal difference and ≥10 considered a clear change or difference. In the present study we looked at the domains of bodily pain, physical function, general health, mental health and vitality. The RAND-36 was registered until 2016 and RAND-12 from 2017 in RevNatus. The scores of the above domains were used.

Statistical analyses

Characteristics of the total JIA cohort and population controls as well as disease-related characteristics of the total JIA cohort, inactive JIA group and active JIA group were reported. Pairwise group comparisons of the total JIA cohort with population controls and the active JIA group with the inactive JIA group were performed using independent samples *t*-test for continuous variables and the Pearson chi-squared test, the Fisher's exact test or the unconditional pooled *z*-test [18] for dichotomous variables.

We report proportions and risk differences for the main outcomes CS, elective CS and emergency CS comparing the total JIA cohort, inactive JIA group and active JIA group one at a time with population controls. We calculated the 95% CI for risk differences using Newcombe's method [19]. Two-sided *P*-values <0.05 were considered to be statistically significant and 95% CIs are reported where relevant. The statistical analyses were performed using SPSS Statistics for Windows version 28.0.1 (Newcombes method, Armonk, NY, USA), Stata MP 17 (StataCorp, College Station, TX, USA) and Exact Unconditional Homogeneity/Independence Tests for 2X2 Tables (https://www4.stat.ncsu.edu/~boos/exact/).

Results

Patient recruitment

There were 199 singleton births among women with JIA registered in RevNatus in 2010 to 2019. Three pregnancies could not be linked to the MBRN, leaving 196 singleton births among women diagnosed with JIA forming the patient group. JIA subtypes are not registered in RevNatus and could not be reported. The population controls amounted to 575 798 singleton births from the general population, excluding births in women diagnosed with inflammatory rheumatic diseases coded according to the ICD-10 (see Supplementary Table S1, available at *Rheumatology Advances in Practice* online).

Characteristics of the patient group and population controls are shown in Table 1. Women with JIA were younger compared with controls. A higher proportion were nulliparous, though not reaching statistical significance. Other characteristics relevant concerning CS did not differ between women with JIA and population controls. Restricting to only women with CS, characteristics of the patient group and population controls did not show relevant differences (see Supplementary Table S2, available at *Rheumatology Advances in Practice* online).

Table 2 presents the disease-related characteristics of all women with JIA and according to inactive and active JIA in pregnancy as assessed by the DAS28-CRP-3. To include as many pregnancies as possible in the disease activity groups, we choose to add patients with registered disease activity in the second trimester when not registered in the third trimester ($n = 21$). Information on disease activity in the second or third trimester was missing in 15 pregnancies. Most women had inactive JIA [131/81 (72.4%)], while 50/181 (27.6%) had active JIA. Erosive disease was more common, and a higher proportion of women with active JIA used prednisolone. The proportions of HCQ, SSZ and TNF inhibitor (TNFi) use were higher in inactive than active disease, although not statistically significant. Other disease-specific medications were not reported to be used during pregnancy in these women.

Table 1. Characteristics of patient groups and population controls

Characteristics	Population controls	JIA	*P*-value[a]
Singleton births, 2010–2019	575 798	196	
Maternal age (years), mean (S.D.)	30.6 (5.1)	29.7 (4.7)	**0.009**
<35	460 720 (80.0)	171 (87.2)	**0.015**
≥35	115 077 (20.0)	25 (12.8)	
Missing	0	0	
Parity			
No children	244 354 (42.4)	97 (49.5)	0.054
≥1 child	331 444 (57.6)	99 (50.5)	
Missing	0	0	
Smoking in pregnancy	34 237 (6.7)	8 (4.3)	0.24
Missing	67 663	10	
BMI (first trimester), mean (S.D.)	24.4 (4.8)	24.3 (4.5)	0.90
≥25.0	138 056 (34.5)	53 (34.4)	1.0
≥30.0	49 167 (12.3)	20 (13.0)	0.89
Missing	176 090		
Previous CS	55 992 (9.7)	25 (12.8)	0.19
Missing	0	0	
Diabetes[b]	25 924 (4.5)	9 (4.6)	1.0
Missing	0	0	
ART	20 121 (3.5)	9 (4.6)	0.52
Missing	0	0	

[a] *P*-value for patient group compared with population controls.
[b] Pre-gestational or gestational.
P-values in bold are significant values (two-sided *P*-values <0.05 are considered statistically significant).

Mental health was assessed as good and in a similar range in both inactive and active JIA, while vitality was assessed as poor in both groups. Mean differences were >10, indicating a clinically relevant difference concerning bodily pain and physical function, favouring inactive disease. Women with inactive and active JIA were similar concerning clinical characteristics when using only third trimester data (see Supplementary Table S3, available at *Rheumatology Advances in Practice* online).

Proportions and risk differences of CS are shown in Table 3. CS occurred more frequently in JIA [40/196 (20.4%)] than in population controls [89 805/575 763 (15.6%)] and most frequently in active JIA [16/51 (31.4%)], with a risk difference of 15.8%. Women with inactive JIA did not have an increased risk of CS compared with population controls.

Table 4 presents results for elective and emergency CS in the patient group and population controls. The proportion of elective CS in JIA [13/196 (6.6%)] was comparable to that of population controls [32 114/575 798 (5.6%)], with no differences concerning inactive or active JIA. Emergency CS occurred more frequently in JIA [27/96 (13.8%)] and was most prominent in active JIA [12/51 (23.5%)] compared with population controls [57 691/575 798 (10.0%)]. The risk difference for emergency CS was 13.5% for women with active JIA compared with population controls, while there was not a

Table 2. Clinical characteristics of JIA, grouped according to disease activity in the second or third trimester

Characteristics	JIA (total)	Inactive JIA (DAS28-CRP-3 <26)	Active JIA (DAS28-CRP-3 ≥2.6)	Diff (*P*-value[a])
Singleton births 2010–2019	196	130	51	
Education level, *n* (%)				
Low (10–13 years)	58 (30.2)	37 (28.9)	16 (32.7)	3.8 (0.76)
High (≥14 years)	134 (69.8)	91 (71.1)	33 (67.3)	
Missing	4	2	2	
Disease criteria fulfilled, *n* (%)	174 (97.2)	115 (97.5)	44 (95.7)	1.8 (0.72)[b]
Missing, *n*	17	12	5	
Disease duration (months), mean (S.D.)	20.2 (7.7)	19.7 (7.5)	22.7 (7.2)	**3.0 (0.033)**
Missing, *n*	40	25	11	
Erosive disease, *n* (%)	68 (42.2)	40 (37.7)	26 (59.1)	**21.4 (0.019)**[b]
Missing, *n*	35	24	7	
Prednisolone in pregnancy, *n* (%)	34 (20.4)	17 (15.5)	17 (37.8)	**22.3 (0.003)**[b]
Missing, *n*	29	20	6	
HCQ in pregnancy, *n* (%)	10 (5.3)	9 (7.2)	1 (2.0)	5.2 (0.21)[b]
Missing, *n*	9	5	2	
SSZ in pregnancy, *n* (%)	17 (9.8)	14 (11.9)	2 (4.5)	7.4 (0.18)[b]
Missing, *n*	22	12	7	
TNFi in pregnancy, , *n* (%)	30 (17.3)	23 (20.0)	5 (10.9)	9.1 (0.18)[b]
Missing, *n*	23	15	5	
Bodily pain[c], mean (S.D.)	60.7 (23.2)	64.4 (22.6)	48.8 (20.7)	**15.6 (<0.001)**
Missing, *n*	46	19	15	
Physical function[c], mean (SD)	63.8 (25.2)	68.6 (23.0)	49.5 (26.6)	**19.1 (<0.001)**
Missing, *n*	46	19	15	
General health[c], mean (S.D.)	58.0 (22.7)	59.4 (23.1)	52.4 (20.8)	7.0 (0.11)
Missing, *n*	46	19	15	
Mental health[c], mean (S.D.)	81.5 (11.8)	81.6 (12.5)	80.2 (9.6)	1.5 (0.52)
Missing, *n*	47	20	15	
Vitality[c], mean (S.D.)	44.2 (20.1)	45.6 (21.1)	38.9 (16.0)	6.7 (0.083)
Missing, *n*	47	20	15	

diff: differences in proportions for dichotomous and mean differences for continuous variables.
[a] *P*-value for active compared with inactive disease.
[b] The unconditional pooled *z*-test.
[c] In the third trimester.
P-values in bold are significant values (two-sided *P*-values <0.05 are considered statistically significance).

Table 3. CS in population controls and patient groups and according to disease activity in the second or third trimester expressed as proportions and risk differences

Groups	Total, *n*	CS, *n*	%	Risk difference, % (95% CI)	*P*-value[a]
Population controls	575 763	89 805	15.6		
JIA, total	196	40	20.4	4.8 (−0.2, 11.0)	0.079
Active	51	16	31.4	15.8 (4.7, 29.4)	**0.004**
Inactive	130	22	16.9	1.3 (−4.1, 8.7)	0.77

[a] *P*-value for patient group compared with population controls. *P*-values in bold are significant values (two-sided *P*-values <0.05 are considered statistically significant).

higher risk in inactive JIA compared with population controls. The same pattern emerged when including third trimester disease activity registrations only, but with no statistically significant results (see Supplementary Tables S4 and S5, available at *Rheumatology Advances in Practice* online).

Discussion

Our study agrees with recent studies in pregnant women with JIA reporting stable disease and remission or low disease activity throughout pregnancy in most of the patients [9, 20–23]. The findings of increased risk for CS in women with JIA compared with population controls are also in line with earlier studies [8–10]. In the present study we found an association of inflammatory active JIA with CS overall and emergency CS, but not elective CS. These are novel findings.

We do not know the indication for emergency CS in our study. In a Norwegian prospective survey, foetal distress and failure to progress were the two main indications for emergency CS [24]. Earlier studies have discussed active disease as a probable contributing factor to the increased risk of CS in women with JIA compared with healthy controls. Remaeus *et al.* [8] reported that JIA persisting into adulthood had the highest mean DAS28-CRP and an increased risk for CS compared with JIA confined to childhood. Both JIA groups had an increased risk for CS compared with population controls, the strongest association being seen with elective CS [22]. One reason for differing conclusions concerning elective CS may be that the Swedish population was from an earlier time period (1992–2011) with a lower threshold for elective CS in women with chronic diseases as well as a higher proportion of women with damaged joints and reduced physical function. In Norway, women with rheumatic diseases are followed according to national guidelines advocating vaginal birth in the absence of obstetric indications [25], and this may be the reason why elective CS is not more frequent in the present study.

In adherence with international guidelines, teratogenic medications were not used in this cohort. However, a high

Table 4. Elective and emergency CS in population controls and patient groups and according to disease activity in the second or third trimester expressed as proportions and risk differences

Group	Total, *n*	Elective CS, *n*	%	Risk difference (95% CI)	*P*-value[a]
Population controls	575 798	32 114	5.6		
JIA, total	196	13	6.6	1.1 (−1.7, 5.4)	0.63
Active	51	4	7.8	2.3 (−2.5, 12.9)	0.53[b]
Inactive	130	8	6.2	0.6 (−2.4, 6.1)	0.92
		Emergency CS, *n*			*P*-value[a]
Population controls	575 798	57 691	10.0		
JIA, total	196	27	13.8	3.8 (−0.4, 9.3)	0.10
Active	51	12	23.5	13.5 (4.0, 26.7)	**0.003**
Inactive	130	14	10.8	0.8 (−3.5, 7.2)	0.89

[a] *P*-value for patient group compared with population controls.
[b] Fisher's exact test. *P*-values in bold are significant values (two-sided *P*-values <0.05 are considered statistically significant).

proportion reported ever using MTX before pregnancy (64.5% in the inactive JIA group and 59.5% in the active JIA group; data not shown). Furthermore, a high proportion reported ever using TNFi before pregnancy (45.1% in the inactive JIA group and 54.1% in the active JIA group; data not shown). Even though we do not know how close to pregnancy these medications were used, it indicates undertreatment in some of the women, resulting in active disease. In the first half of the study period, the recommendations on TNFi use in pregnancy were stricter due to little documentation, probably contributing to the lower proportions of treatment in pregnancy.

Women with active JIA expressed more pain and lower physical function, possibly contributing to the decision for CS in cases where other risk factors were present. However, we assume this might be most relevant for the decision for elective, and not emergency, CS.

Strengths of the study include the prospective follow-up, the large patient group, linkage of two registries and assessment of disease activity during pregnancy. A limitation is that there are no validated disease activity assessments for pregnant women with JIA. The DAS28-CRP-3 was used, as it avoids ESR and patient global, which may both be influenced by the pregnancy itself. It has been validated for use in pregnant women with RA [13] and is regarded as reliable for assessing disease activity in pregnant women with JIA [26]. Another limitation may be that women with quiescent disease or with no medication are not included in the register, thus missing women with inactive disease or low disease activity. This might overestimate the proportion of women with active disease.

We believe the register to be representative of the population at large, as most pregnant women with inflammatory rheumatic diseases in Norway are followed in the public specialist healthcare system and enrolled in RevNatus.

Conclusion

Women with active JIA in the second part of pregnancy had a higher risk for emergency CS than population controls in a prospective cohort. This underlines that treat to target with the goal of remission is an important strategy in pregnant women with rheumatic diseases.

Supplementary material

Supplementary material is available at *Rheumatology Advances in Practice* online.

Data availability

The data cannot be shared publicly due to the requirements of the involved register holders and the general data protection regulation, to protect the privacy of individuals.

Authors' contributions

All authors planned the study. CGS and SL analysed and all authors interpretated the data. CGS and MW drafted the paper. All authors contributed to editing the draft for content, approved the final version and have agreed to be accountable for all aspects of the work.

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