Pregnancy outcome in joint hypermobility syndrome and Ehlers–Danlos syndrome

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Key words
Joint hypermobility syndrome, Ehlers–Danlos syndrome, pregnancy, child, obstetric – cohort study

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Conflict of interest
The authors have stated explicitly that there are no conflicts of interest in connection with this article.


Abstract

Introduction. An increased risk of preterm birth in women with joint hypermobility syndrome or Ehlers–Danlos syndrome is suspected. Material and methods. In this nationwide cohort study from 1997 through 2011, women with either joint hypermobility syndrome or Ehlers–Danlos syndrome or both disorders were identified through the Swedish Patient Register, and linked to the Medical Birth Register. Thereby, 314 singleton births to women with joint hypermobility syndrome/Ehlers–Danlos syndrome before delivery were identified. These births were compared with 1,247,864 singleton births to women without a diagnosis of joint hypermobility syndrome/Ehlers–Danlos syndrome. We used logistic regression, adjusted for maternal age, smoking, parity, and year of birth, to calculate adjusted odds ratios for adverse pregnancy outcomes. Results. Maternal joint hypermobility syndrome/Ehlers–Danlos syndrome was not associated with any of our outcomes: preterm birth (adjusted odds ratio = 0.6, 95% confidence interval 0.3–1.2), preterm premature rupture of membranes (adjusted odds ratio = 0.8; 95% confidence interval 0.3–2.2), cesarean section (adjusted odds ratio = 0.9, 95% confidence interval 0.7–1.2), stillbirth (adjusted odds ratio = 1.1, 95% confidence interval 0.2–7.9), low Apgar score (adjusted odds ratio = 1.6, 95% confidence interval 0.7–3.6), small for gestational age (adjusted odds ratio = 0.9, 95% confidence interval 0.4–1.8) or large for gestational age (adjusted odds ratio = 1.2, 95% confidence interval 0.6–2.1). Examining only women with Ehlers–Danlos syndrome (n = 62), we found a higher risk of induction of labor (adjusted odds ratio = 2.6; 95% confidence interval 1.4–4.6) and amniotomy (adjusted odds ratio = 3.8; 95% confidence interval 2.0–7.1). No excess risks for adverse pregnancy outcome were seen in joint hypermobility syndrome. Conclusion. Women with joint hypermobility syndrome/Ehlers–Danlos syndrome do not seem to be at increased risk of adverse pregnancy outcome.

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; EDS, Ehlers–Danlos syndrome; ICD, International Classification of Diseases; JHS, joint hypermobility syndrome; PPROM, preterm premature rupture of fetal membranes; SGA, small for gestational age.

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Introduction

Many risk factors for adverse pregnancy outcome are dependent on the uterus, birth channel and membranes, which, in turn, rely on well-functioning connective tissue. Ehlers–Danlos syndrome (EDS) is a genetic (predominantly dominant autosomal) disorder caused by dysfunctional collagen, the main type of protein in connective tissue (1). Joint hypermobility syndrome (JHS) most commonly represents a subtype of EDS and likely shares the same genetic background (2,3). Patients with JHS/EDS have hypermobile joints and hyperextensive skin and can present with symptoms from a large number of organs (1), including bleeding (4).

We are aware of three earlier studies on pregnancy outcome in EDS. All three were based on retrospective questionnaires and reported a prevalence of preterm birth exceeding 21% (5–7). Furthermore, one Italian study of 82 women with JHS found that 13.9% of the offspring were born preterm with more than one in five women having a cesarean section (8). Preterm premature rupture of membranes (PPROM) has been suggested to be the leading cause of preterm birth in women with JHS and EDS (7–10).

As a result of the three studies based on questionnaires, it is recommended that women with JHS/EDS receive counseling before pregnancy and are closely monitored during pregnancy (5,7). It should also be noted that women with JHS/EDS often suffer pain in general (11) as well as during pregnancy, which might result in a deterioration of the mother’s (and possibly the fetus’s) well-being.

There are no studies reporting Apgar score or birthweight of the offspring according to gestation. We conducted a study to analyze the risk of adverse pregnancy outcome in women with JHS and EDS. We hypothesized that maternal JHS/EDS was a risk factor for adverse pregnancy outcome.

Material and methods

This study includes births to women diagnosed with JHS or EDS according to the Swedish Patient Registry. The Swedish Patient Registry started in 1964 and became nationwide in 1987 (12). Since 2001, the Swedish Patient Registry includes hospital-based outpatient care as well as data on hospital admissions and today covers more than 99% of all hospital discharges. We identified all singleton births from 1997 until the end of 2011 in the Swedish Medical Birth Registry and linked them to the Swedish Patient Registry through the unique personal identity number assigned to all residents of Sweden (13). The Medical Birth Registry started in 1973 and 98.6% of all infants born in Sweden are recorded in the register (14). In the register there is a wide range of information regarding pregnancy and neonatal outcome. According to a validation of the register in 2001, included variables have a high validity (14). Diagnoses of EDS and JHS (Q79.6 and M35.7, respectively) were first introduced formally in the 10th revision of the International Classification of Disease (ICD-10), which was implemented in Sweden 1997. We therefore restricted our participants to births from 1997 and later.

We analyzed data for births to women with either JHS or EDS or both disorders (“JHS/EDS”) and for EDS separately. Singleton births to women who had never had a diagnosis of EDS or JHS were used as controls.

Data on smoking, height and weight at the first maternity visit, maternal disease, maternal country of birth, parity, onset of delivery, mode of delivery, completed weeks of gestation, PPROM, amniotomy, stillbirth, Apgar scores, offspring sex and birthweight were extracted from the Medical Birth Registry recorded during the first antenatal visit and throughout the pregnancy and perinatal period.

Body mass index was calculated using weight and height from the first antenatal visit. Until 2008, stillbirth was defined as fetal death at ≥28 completed gestational weeks and thereafter from 22 gestational weeks or later, small for gestational age (SGA) birth as having a birth weight of more than two standard deviations below the mean birthweight, and large for gestational age birth as having a birthweight of two standard deviations above the mean birth weight for their gestational age according to the Swedish sex-specific fetal growth curve. Preterm birth was defined as <37 completed weeks of gestation (15) and Apgar score as Apgar <7 at five minutes. Data on PPROM was registered according to ICD-10 diagnosis O42, and amniotomy (MAC00) according to the Swedish version of NOMESCO (Classification of Surgical Procedures Version 1.9).

We calculated crude and adjusted odds ratios (ORs, aORs) with 95% confidence intervals (CIs) using unconditional logistic regression. We adjusted for maternal age at delivery (≤24, 25–29, 30–34, ≥35 years), maternal country of birth, calendar year of birth, smoking (yes vs. no), parity (primipara or multipara), and maternal body

Key Message

There is no risk of adverse pregnancy outcomes in joint hypermobility syndrome or Ehlers–Danlos syndrome.
mass index in early pregnancy (≤19, 20–24, 25–29, ≥30). Data were analyzed using SPSS software, version 22 (IBM Corp., Armonk, NY, USA).

The study was approved by the Regional Ethics Committee in Stockholm, Sweden (Protocol no. 2008/4:7).

Results

We identified 314 singleton births to women with EDS (n = 62) and JHS (n = 260) diagnosed before delivery from the Swedish National Patient Registry. Eight women were diagnosed with both JHS and EDS. In the control group, there were 1,247,864 singleton births.

There was no significant difference between women with EDS or JHS/EDS and the control group median age at delivery, parity, offspring sex, body mass index or maternal country of birth (Table 1). A higher proportion of women with JHS/EDS were smokers (Table 1).

<table>
<thead>
<tr>
<th>Maternal age, years</th>
<th>EDS (n = 62)</th>
<th>JHS/EDS (n = 314)</th>
<th>Controls (n = 1,247,864)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤24</td>
<td>8</td>
<td>12.9</td>
<td>11.9</td>
</tr>
<tr>
<td>25–29</td>
<td>18</td>
<td>29.0</td>
<td>31.8</td>
</tr>
<tr>
<td>30–34</td>
<td>20</td>
<td>32.3</td>
<td>33.8</td>
</tr>
<tr>
<td>≥35</td>
<td>16</td>
<td>25.8</td>
<td>20.4</td>
</tr>
</tbody>
</table>

Parity

Primipara

Multipara

42          | 67.7        | 179           | 45.6        |

Maternal country of birth

Nordic

Non-nordic

6           | 9.7         | 221           | 17.8        |

BMI

≤19

20–24

25–29

≥30

9           | 14.5        | 27            | 8.6         |

Sex, offspring

Female

Male

45          | 54.8        | 606           | 48.6        |

34          | 54.8        | 641           | 51.4        |

Calendar year of birth

1997–2001

2002–2006

2007–2011

3           | 4.8         | 350           | 28.1        |

14          | 22.6        | 411           | 33.0        |

45          | 72.6        | 485           | 38.9        |

Smoking in early pregnancy

Non-smoker

1–9 Cigarettes/day

≥10 Cigarettes/day

52          | 83.9        | 1,343         | 90.9        |

6           | 9.7         | 81            | 6.6         |

4           | 6.5         | 31            | 2.5         |

EDS, Ehlers-Danlos syndrome; JHS, joint hypermobility syndrome; BMI, body mass index.

None of the EDS women had PPROM, which can be compared with 4/314 (1.3%) of the JHS/EDS women and 18/952/1,247,864 (1.5%) of the controls (Table 2). We found an increased risk of labor induction in women with EDS (aOR = 2.6; 95% CI 1.4–4.6) but this association was not statistically significant for JHS/EDS (Table 2). The risk of amniotomy was significantly increased in women with EDS (aOR = 3.8; 95% CI 2.0–7.1) (Table 2) but not in women with JHS/EDS. The rates of cesarean section delivery were similar in women with EDS, JHS/EDS and controls (Table 2). JHS/EDS was not associated with stillbirth (aOR = 1.1; 95% CI 0.2–7.9) (Table 2). Two of 62 (3.2%) EDS births and 10 of 314 (3.2%) JHS/EDS births were preterm compared with 60/1,247,864 (4.9%) control births (Table 2). Neither EDS nor JHS/EDS was associated with preterm birth (Table 2). None of the offspring to women with EDS had an Apgar score <7 at five minutes, compared with 1.9% of the offspring to women with JHS/EDS and 1.2% of the controls (Table 2). The prevalence of SGA birth was 3.2% in EDS pregnancies, 2.6% in JHS/EDS pregnancies and 2.7% in control pregnancies (Table 2). There was no increased risk of large for gestational age birth in offspring to women with EDS or JHS/EDS (Table 2).

Discussion

In this nationwide population-based study of more than 300 births to women with JHS/EDS, we found no increased risk of adverse pregnancy outcome.

Preterm delivery was only seen in 3.2% of the Swedish women with JHS/EDS vs. 4.9% of the controls. Two studies from the USA, one excluding women with type IV EDS, found a preterm birth rate of 23.1% (6) and another study (where 4.8% of the women had type IV EDS) reported a rate of 25.2% [as compared with 12% in the US general population (16)]. A study in the Netherlands (7) reported preterm birth in 21.9% of the women with EDS vs. 4.9% of the controls (vs. 8% in the general population (16)). In contrast to the current study, earlier studies have found a positive association between EDS and preterm delivery. However, these studies are likely to suffer from selection bias, as they were based on data from online questionnaires and questionnaires sent to members of patient organizations for people with JHS/EDS. If women experiencing difficulties in their pregnancies were more likely to respond to the questionnaires, this selection bias would have increased the risk estimates and the prevalence of adverse pregnancy outcome in EDS. The study from the Netherlands also evaluated pregnancies in women without EDS retrospectively, where the fetuses were later diagnosed with EDS. The authors found that 40% of the fetuses were delivered preterm (7).
Another study found Ehlers–Danlos-like dermal abnormalities in women (without diagnosed EDS) with PPROM (10). Based on these findings, a review article suggested that the fetus per se might contribute to PPROM through genes linked to classical types of EDS among other connective tissue disorders (17).

Because JHS/EDS has a predominantly autosomal dominant inheritance, approximately half of the infants born to women with JHS/EDS in our cohort would have inherited the condition. We found no case of PPROM in the EDS group, and the same PPROM rate in our JHS group as in the control group (26.2% of preterm controls). A recent study on the causes of preterm births found PPROM to be the cause in 22% of preterm pregnancies (18). We found a 2.6-fold increased risk of induction and a 3.8-fold increased risk of amniotomy in our EDS group. These findings might suggest a dysfunction either in the membranes or in the muscles involved in labor, or might be due to a wish to accelerate the birth process because of unknown circumstances. Individuals with EDS have dysfunctional connective tissue and therefore excessive enlargement of the uterus might more easily cause a loss in strength in the same organ.

The indication for cesarean section varies between countries and between clinics within the same country. Our patients had their deliveries in hospitals throughout Sweden, a country with a rather uniform health care service. We found no evidence of an increased risk of cesarean delivery in the women with JHS/EDS in comparison with the controls. In an Italian study of 82 patients with JHS, 22.3% were delivered with cesarean section and 13.9% were delivered preterm (8). In Italy, however, the cesarean section rate is above 30% and varies greatly between clinics (19). Hence, the data from JHS women in Italy may not represent an increase. One US study reported a cesarean delivery rate of 8.4% in women with EDS (6), in line with our results (i.e. no increased risk, or even a negative association) considering that the rate of cesarean section in the US general population is above 30% (20).

Table 2. Perinatal adverse events in women with EDS, JHS and JHS/EDS combined.

<table>
<thead>
<tr>
<th>Event</th>
<th>Cases in patients</th>
<th>Cases in controls</th>
<th>Crude OR; 95% CI</th>
<th>Adjusted OR (^a); 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm birth</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDS</td>
<td>2/62</td>
<td>60 659/1 248 116</td>
<td>4.9</td>
<td>0.6; 0.2–2.7</td>
</tr>
<tr>
<td>JHS+EDS</td>
<td>10/314</td>
<td>60 651/1 247 864</td>
<td>4.9</td>
<td>0.6; 0.3–1.2</td>
</tr>
<tr>
<td>PPROM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDS</td>
<td>0/62</td>
<td>18 956/1 248 116</td>
<td>1.5</td>
<td>NC</td>
</tr>
<tr>
<td>JHS+EDS</td>
<td>4/314</td>
<td>18 952/1 247 864</td>
<td>1.5</td>
<td>0.8; 0.3–2.2</td>
</tr>
<tr>
<td>Induction of labor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDS</td>
<td>16/62</td>
<td>140 045/1 248 116</td>
<td>11.2</td>
<td>2.8; 1.6–4.9</td>
</tr>
<tr>
<td>JHS+EDS</td>
<td>43/314</td>
<td>140 018/1 247 864</td>
<td>11.2</td>
<td>1.3; 0.9–1.7</td>
</tr>
<tr>
<td>Amniotomy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDS</td>
<td>12/62</td>
<td>54 136/1 248 116</td>
<td>4.3</td>
<td>5.3; 2.8–9.9</td>
</tr>
<tr>
<td>JHS+EDS</td>
<td>27/314</td>
<td>54 121/1 247 864</td>
<td>4.3</td>
<td>2.1; 1.4–3.1</td>
</tr>
<tr>
<td>Cesarean section</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDS</td>
<td>8/62</td>
<td>194 330/1 248 116</td>
<td>15.6</td>
<td>0.8; 0.4–1.7</td>
</tr>
<tr>
<td>JHS+EDS</td>
<td>46/314</td>
<td>194 292/1 247 864</td>
<td>15.6</td>
<td>0.9; 0.7–1.3</td>
</tr>
<tr>
<td>Stillbirth</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDS</td>
<td>0/62</td>
<td>3656/1 248 116</td>
<td>0.3</td>
<td>NC</td>
</tr>
<tr>
<td>JHS+EDS</td>
<td>1/314</td>
<td>3655/1 247 864</td>
<td>0.3</td>
<td>1.1; 0.2–7.8</td>
</tr>
<tr>
<td>Apgar score &lt;7 at 5 min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDS</td>
<td>0/61</td>
<td>14 613/1 238 456</td>
<td>1.2</td>
<td>NC</td>
</tr>
<tr>
<td>JHS+EDS</td>
<td>6/313</td>
<td>14 607/1 238 204</td>
<td>1.2</td>
<td>1.6; 0.7–3.7</td>
</tr>
<tr>
<td>SGA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDS</td>
<td>2/62</td>
<td>34 173/1 244 007</td>
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</tr>
<tr>
<td>JHS+EDS</td>
<td>8/313</td>
<td>34 167/1 243 756</td>
<td>2.7</td>
<td>0.9; 0.5–1.9</td>
</tr>
<tr>
<td>LGA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDS</td>
<td>3/62</td>
<td>43 067/1 244 007</td>
<td>3.5</td>
<td>1.4; 0.4–4.5</td>
</tr>
<tr>
<td>JHS+EDS</td>
<td>11/313</td>
<td>43 059/1 243 756</td>
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<td>1.0; 0.6–1.8</td>
</tr>
</tbody>
</table>

EDS, Ehlers–Danlos syndrome; JHS, joint hypermobility syndrome; OR, odds ratio; CI, confidence interval; PPROM, preterm premature rupture of membranes; SGA, small for gestational age; LGA, large for gestational age; NC, not calculated.

\(^a\)ORs were adjusted for maternal age, country of maternal birth, smoking, body mass index, parity, and year of birth. Statistically significant risk estimates are italicized.

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Despite the significantly increased risk of induced labor in EDS, lower Apgar scores were not more prevalent than in the general population, a finding consistent with an Italian study that failed to demonstrate an increase in neonatal hypoxia in offspring of EDS women (8).

The risk of SGA births was not increased in our study population. Although we are unaware of any previous study on pregnancy outcome in JHS/EDS, a study on women with another connective tissue disease (fibromyalgia) (21) reported a positive association with intrauterine growth retardation but not with SGA or higher rates of preterm birth (21).

The main strengths of our study are the population-based design, the large number of JHS/EDS women, and our adjustment for confounding factors. Our study is likely to have identified a high proportion of pregnant women with JHS/EDS. Although we cannot rule out some false-negative cases, they should not have affected our risk estimates more than marginally, as JHS/EDS is rare in the general population. What is probably more serious is that women with severe JHS/EDS are more likely to be detected than are women with mild disease. Despite this potential shortcoming, we found no association between JHS/EDS and adverse pregnancy outcome.

One weakness of our study is the lack of validation of the JHS and EDS diagnoses in the Swedish Patient Registry; however, the positive predictive value of most chronic disorders in the Swedish Patient Registry is about 85–95% (12).

We used the ICD-10 classification, in which JHS and EDS are two different disorders; hence we cannot say for certain that JHS is a subtype of EDS. Other weaknesses are our lack of data on type of EDS and being unable to differentiate between non-vascular and vascular EDS. There are many other rare subtypes of EDS as well and more are being added regularly. Many of these rare subtypes have very obvious and different symptoms than the more common types of EDS. Because of the infrequency of these subtypes, it is difficult to draw firm conclusions about symptoms and consequences of pregnancy in women with JHS/EDS.

In conclusion, this population-based study found no association between JHS/EDS and adverse pregnancy outcome (such as preterm birth and cesarean section). We observed that induction of labor and amniotomy were slightly more prevalent in women with EDS, which might indicate dysfunctional connective tissue but without consequences for pregnancy outcome.

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**References**


