Impaired reproductive fitness in mothers of children with juvenile autoimmune arthropathies

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Objective. To assess the reproductive fitness of mothers of children with juvenile idiopathic arthritis (JIA). Methods. A mail survey assessing pregnancy outcome was carried out among mothers of children with JIA (JIA mothers) treated at a tertiary paediatric rheumatology centre. The best friends of the JIA mothers served as controls. Besides family history, sociodemographics and reproductive outcomes were measured, including the number of pregnancies, pregnancy complications and gestational age at the time of delivery.

Results. JIA mothers (n = 227) and controls (n = 235) had similar sociodemographics and racial backgrounds. On average, JIA mothers reported a greater number of conceptions than controls (3.5 vs 3.1; P = 0.01) but had significantly higher rates of pregnancy complications (25% vs 15%; P < 0.001). Corrected for differences in the absolute number of pregnancies between groups, the chances of having a miscarriage [mean (s.d.), 0.12 (0.18) vs 0.09 (0.16); P = 0.02] or preterm delivery [0.08 (0.21) vs 0.04 (0.15); P < 0.02] were significantly greater among JIA mothers than controls.

Conclusions. Mothers of children with JIA have impaired reproductive fitness. This phenomenon is unlikely to be the result of difficulty with conception but rather to be due to higher rates of pregnancy loss and premature delivery.

Key words: Maternal reproductive fitness, Conception, JIA, JRA, Childhood autoimmunity, Pregnancy loss.

Childhood autoimmune arthropathies are a group of diseases classified as juvenile idiopathic arthritis (JIA) [1], also known as juvenile rheumatoid arthritis (JRA) [2], whose histological hallmark is infiltration of the synovium by activated immune cells. These arthropathies, henceforth simply referred to as JIA, are associated with clonal expansion of T-lymphocytes and the presence of autoantibodies, including antinuclear antibodies.

The aetiology of JIA is unknown, but previous research supports the notion that disease susceptibility is based on one or more complex genetic traits [3], which are in part shared with other autoimmune diseases. Data supporting familial aggregation of JIA are limited, and consist primarily of reports of affected sib pairs [4–6]. Besides increased prevalence of JIA, a higher prevalence of other autoimmune diseases has also been reported in families of children with JIA [7]. Similar phenomena have been observed in families of patients with other forms of autoimmunity, including autoimmune thyroid disease, type 1 diabetes, alopecia areata and vitiligo [8–10]. Chromosome regions marked by polymorphic variants in common with several autoimmune diseases have been identified [11], and specific polymorphisms have been found in a number of genes that are potential contributors to this autoimmune trait, including CTLA4, MIF, NRAMP and PTPN22 [12–17]. Impaired reproductive fitness has been reported for patients with several different forms of autoimmunity [18, 19]. The possibility that the familial autoimmune trait, of which JIA is part, and impaired reproductive fitness are related and therefore not limited to the patient prompted us to assess the reproductive history of mothers of children with JIA.

Materials and methods

Study participants

Mothers of children with JIA. Following approval by the Institutional Review Board and the treating paediatric rheumatologists, mothers of children with JIA currently or previously treated at the Cincinnati Children’s Hospital Medical Center were invited to participate in this study of reproductive history. Invitations were sent via US mail and mothers of children with JIA (JIA mothers) who agreed and signed a written consent form were included in the study. In addition, these mothers were asked to provide the names of three of their best friends to serve as potential controls in the study.

Best-friend controls. The best-friend approach [18, 20] was taken to control for sociodemographic factors such as race, income, education and marital status, some of which may influence reproductive history. Best friends named by a JIA mother were randomly selected from the available candidates by two of the investigators (M.C., M.M.) and invited to participate in the study. To be included, best-friend controls had to meet the following criteria: (i) provision of written consent to participate in the study; (ii) self-reported race identical with the referring JIA mother; (iii) age within 10 yr of the referring JIA mother’s age; and (iv) a history of having given birth to at least one child. Excluded were controls having a child with JIA.

Mail survey of reproductive fitness

Study participants were asked to independently complete the Reproductive Fitness Questionnaire (RFQ). This standardized

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Submitted 2 November 2005; revised version accepted 17 February 2006.

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questionnaire consists of two sections. Section 1 enquires about the participant’s sociodemographics and Section 2 addresses the reproductive fitness of the participant. The items for this RFQ section were selected from two widely validated [21] instruments, the National Survey of Family Growth [22] and the American College of Obstetricians and Gynecologists (ACOG) Antepartum Record and Discharge/Postpartum Form (http://www.acog.com).

Measures of reproductive fitness. In the absence of a universally accepted measure of reproductive fitness, several reproductive outcomes were measured in the RFQ. Besides the total number of pregnancies (conceptions), the outcome of each pregnancy was assessed. Specific pregnancy outcomes surveyed were: (i) miscarriages, i.e. spontaneous abortions prior to the 20th week of gestation (dated from the first day of last normal menstrual period); (ii) preterm deliveries, i.e. pregnancies resulting in an infant born with a gestational age of 20–36 weeks dated from the first day of last normal menstrual period; (iii) Stillbirth, i.e. a pregnancy resulting in an infant who died prior to a delivery that occur after 5 or more months of pregnancy; and (iv) termination of the pregnancy by elective abortion for non-medical reasons. Birth of a full-term infant was considered the expected normal pregnancy outcome. Conversely, all other pregnancy outcomes (excluding pregnancies that ended in elective abortions for non-medical reasons) were considered as pregnancy complications. In addition, data were collected for all pregnancies for the following events: vaginal bleeding during the first 6 months, vaginal bleeding after the first 6 months, anaemia related to pregnancy, diabetes related to pregnancy and pregnancy-related high blood pressure (also called pre-eclampsia).

Statistical analysis

Data were analysed using SAS 8.2 (SAS, Cary, NC, USA) and Excel (Microsoft, Redmond, WA, USA). In this case–control study, mothers of children diagnosed with JIA were compared with a cohort of females drawn from a pool of JIA mother’s best friends provided by participating JIA mothers. The statistical analysis was guided by the objectives of the study, i.e. to test whether there were significant differences between JIA mothers and the best-friend controls with regard to reproductive fitness measures. JIA mothers were compared with the best-friend control mothers using Student’s t-test or the Wilcoxon rank sum test for continuous variables. Kruskal-Wallis test was used depending on the variance and the Kurtosis of the data. Differences in categorical data between groups were assessed for statistically important differences using either the χ² test or Fisher’s exact test, as appropriate. The rates of pregnancy complications (miscarriage, preterm, stillbirth or any of the three) were calculated by dividing the total number of pregnancies with these pregnancy complications by the total number of pregnancies for each mother. Of note, electively terminated pregnancies for non-medical reasons (abortions) were excluded from the analysis of pregnancy complications. For a given participant, pregnancy outcomes were not considered independent events. Therefore, to test for important differences in reproductive outcome between JIA mothers and controls, generalized estimation equations (GEE) analysis was used to take into account the correlation of pregnancy outcomes for a given participant.

Results

Study cohort and survey response rates

Study invitation letters were mailed to 461 JIA mothers. We were unable to reach 113 (25%) of the total. Of the remaining eligible JIA mothers, 91% (316/348) agreed to participate in the study. Completed RFQs were returned by 72% (227/316) of JIA mothers and 60% (136/227) provided contact information for a potential ‘best-friend’ control. Of the total number of 372 best friends contacted, 63% (235/372) returned the completed RFQ. Some JIA mothers refused to provide contact information for potential best-friend controls, the most frequent reason being that the JIA mothers felt uncomfortable asking their friend to participate. Few participants contacted the study personnel for help with answering RFQ questions thus, supporting the face validity of the instrument.

The best-friend sample strategy yielded JIA mothers and controls who were well matched for sociodemographic factors, some of which may affect reproductive fitness (Table 1). Study and control participants did not differ in age at the time of the study. JIA mothers and controls were on average 46.2 and 45.9 yr old, respectively (Wilcoxon rank sum test; P = 0.92). These groups also had a similar composition with regard to socio-economic status, as measured by family income and the highest level of formal education, and did not differ in the frequency of factors that more directly affect reproductive outcome, including marital status, age at menarche and age at initiation of sexual activity. Maternal mean age at the time of first pregnancy was about 1 yr younger in JIA mothers than in the control group mean ± S.D. (24.10 ± 4.05 vs 25.52 ± 4.62 yr; Wilcoxon rank sum test; P = 0.002), while their age at last pregnancy was about the same mean ± S.D. (31.51 ± 5.22 vs 31.10 ± 4.72 for JIA mothers and controls, respectively; Wilcoxon rank sum test, P = 0.40). Thirty-seven (17.8%) JIA mothers and twenty-eight (12.8%) control mothers had their first pregnancy before age 20 (χ² test, P = 0.15). On the other hand, only one JIA mother (0.48%) compared with six (2.74%) control mothers had their first pregnancy after age 35 (χ² test, P = 0.06). Considering repeated pregnancies within mothers, we conducted GEE analysis to compare maternal ages at conception between the two groups. The analyses did not identify significant group differences (P = 0.22).

JIA mothers appear to have no difficulty with conception

The 227 JIA mothers reported a total of 796 compared with 717 pregnancies for the 235 best-friend controls. These counts include pregnancies that ended in elective abortions for non-medical reasons. Thus, JIA mothers reported significantly more pregnancies per subject than controls (mean ± S.D., 3.50 ± 1.67 vs 3.05 ± 1.22; Kruskal-Wallis test, P = 0.01), indicating the absence of infertility or difficulty conceiving in this population. Forty-six of 227 (20%) of JIA mothers reported five or more pregnancies, compared with 26 of 235 (11%) control mothers (χ² test; P = 0.009). JIA mothers had, in addition to a greater number of pregnancies, longer total reproductive histories, as measured by family income and the highest level of formal education, and did not differ in the frequency of factors that more directly affect reproductive outcome, including marital status, age at menarche and age at initiation of sexual activity. Maternal mean age at the time of first pregnancy was about 1 yr younger in JIA mothers than in the control group mean ± S.D. (24.10 ± 4.05 vs 25.52 ± 4.62 yr; Wilcoxon rank sum test; P = 0.002), while their age at last pregnancy was about the same mean ± S.D. (31.51 ± 5.22 vs 31.10 ± 4.72 for JIA mothers and controls, respectively; Wilcoxon rank sum test, P = 0.40). Thirty-seven (17.8%) JIA mothers and twenty-eight (12.8%) control mothers had their first pregnancy before age 20 (χ² test, P = 0.15). On the other hand, only one JIA mother (0.48%) compared with six (2.74%) control mothers had their first pregnancy after age 35 (χ² test, P = 0.06). Considering repeated pregnancies within mothers, we conducted GEE analysis to compare maternal ages at conception between the two groups. The analyses did not identify significant group differences (P = 0.22).

JIA mothers have higher rates of pregnancy loss and preterm delivery

As mentioned above, there were 796 pregnancies among JIA mothers and 717 among controls. Twenty (2.51%) pregnancies of JIA mothers and 15 (2.09%) pregnancies of controls ended in elective abortion for non-medical reasons. No group differences

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were found ($\chi^2$ test, $P = 0.49$; GEE, $P = 0.53$). These 35 pregnancies that ended in elective abortion for non-medical reasons were excluded from the subsequent analysis.

Compared with controls, JIA mothers reported more pregnancy losses (miscarriages and stillbirths) and preterm deliveries (25 vs 15%; $\chi^2$ test, $P < 0.001$) (Table 2). The same observation held true when corrections for repeated pregnancies for the same subject were applied (the rates of pregnancy loss and preterm delivery were 0.20 and 0.13 for JIA mothers and controls, respectively) (Table 3). Taken together, JIA mothers were at a significantly higher risk of encountering these pregnancy complications than controls (Wilcoxon rank sum test, $P = 0.001$). Of note, no mother in either group reported recurrent abortions, i.e. three or more spontaneous miscarriages.

**Morbidity and exposures during pregnancy as possible reasons for differences in reproductive fitness between groups**

Subsequently we screened for possible reasons that could account for the observed differences in the pregnancy outcomes of JIA mothers and controls (Table 4). Morbid conditions investigated by the RFQ were development of diabetes, vaginal bleeding, anaemia and/or hypertension. There was a trend towards a greater risk of pregnancy-related high blood pressure and vaginal bleeding during the first semester in JIA mothers. Exposures addressed in this study included cigarette smoking and alcohol abuse during pregnancy. JIA mothers did not differ significantly from controls for either. Therefore, the differences in reproductive fitness cannot be attributed to these exposures.

**Discussion**

We provide epidemiological evidence of significantly impaired reproductive fitness among mothers of children with JIA.
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Table 4. Exposures and pregnancy-related events of JRA mothers and best-friend controls

<table>
<thead>
<tr>
<th></th>
<th>JIA mothers (N = 227)</th>
<th>Controls (N = 235)</th>
<th>Odds ratio (95% CI)</th>
<th>P-valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of contraceptive use</td>
<td>211 (93)</td>
<td>226 (97)</td>
<td>0.50 (0.21, 1.20)</td>
<td>0.1</td>
</tr>
<tr>
<td>Cigarette smoking during pregnancy</td>
<td>21 (9)</td>
<td>23 (10)</td>
<td>0.94 (0.50, 1.75)</td>
<td>0.8</td>
</tr>
<tr>
<td>Alcohol use during pregnancy</td>
<td>10 (4)</td>
<td>7 (3)</td>
<td>1.50 (0.56, 4.01)</td>
<td>0.4</td>
</tr>
<tr>
<td>Vaginal bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st and 2nd trimesters</td>
<td>75 (33)</td>
<td>58 (24)</td>
<td>1.50 (1.00, 2.24)</td>
<td>0.05</td>
</tr>
<tr>
<td>3rd trimester</td>
<td>18 (8)</td>
<td>11 (5)</td>
<td>1.75 (0.81, 3.79)</td>
<td>0.2</td>
</tr>
<tr>
<td>Anaemia related to pregnancy</td>
<td>54 (24)</td>
<td>47 (20)</td>
<td>1.25 (0.80, 1.94)</td>
<td>0.3</td>
</tr>
<tr>
<td>Diabetes related to pregnancy</td>
<td>14 (6)</td>
<td>13 (6)</td>
<td>1.12 (0.52, 2.44)</td>
<td>0.8</td>
</tr>
<tr>
<td>Hypertension related to pregnancy</td>
<td>27 (12)</td>
<td>16 (7)</td>
<td>1.84 (0.96, 3.32)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

aχ² test.
bAlso known as pre-eclampsia.

These mothers had a higher absolute number of pregnancies per mother than controls, arguing against difficulty with conception. At least for the pregnancy complications included in this assessment, JIA mothers were found to have higher risk, even after correction for the number of pregnancies per group. These results are consistent with earlier findings of altered sibship size in JIA families [23] and with previous reports of reduced reproductive fitness in women carrying a diagnosis of an autoimmune disease. For example, patients with SLE have the most striking difficulties with pregnancy and are similar to the JIA mothers reported here; fetal loss and preterm delivery are common. Many of the problems in SLE pregnancies have been attributed to the presence of antiphospholipid antibodies (APLA) [19, 24]. In addition, excess fetal loss has been reported in both rheumatoid arthritis and scleroderma patients. Reproductive impairment is also observed in patients with non-rheumatic autoimmune diseases, such as type I diabetes and thyroiditis. The extent to which APLA are involved in reproductive impairment in autoimmune diseases other than SLE remains to be determined. Previous research indicates that a diagnosis of SLE is rare among JIA mothers [7] and only one JIA mother and one control in this series reported having been diagnosed with SLE. This suggests that mechanisms of impaired reproductive fitness observed among JIA mothers are different from those seen in SLE. Certain immunological mechanisms have also been invoked in a variety of pregnancy-related disorders, of which recurrent spontaneous miscarriages have probably been best studied [25, 26]. Immunological factors involved in reproductive fitness impairment include sharing of HLA alleles by the parents and the presence of allelic variants of HLA-G that are associated with impaired reproductive fitness [27, 28]. Spontaneous miscarriages are probably associated with cytokine dysregulation and changes in the endocrine environment [29, 30].

One interesting explanation for these events would be the presence of different pathologies at the placental level that can modulate the fetus’s developing immune system. These might include any source of inflammation that causes an exacerbation of the normal state of mild systemic inflammation seen in pregnancy [31]. It is possible that these states are due to infections or as complications of immunologically related diseases. In this context it is noteworthy that chronic placentitis or villitis has been found more often among mothers themselves diagnosed with an autoimmune disease [32–34]. Although this may not be the single cause, it is possible that inflammation not only compromises pregnancy outcome but, in addition, the associated prenatal inflammatory milieu could alter the normal development of the fetal immune system. There are several studies that support the relationship between the intrauterine environment and postnatal health [35, 36]. Low birth weight itself is associated with the subsequent development of inflammatory and non-inflammatory diseases such as coronary heart disease, stroke, hypertension, diabetes and spinal osteophtosis [37–39].

Thus, it is possible to consider a two-stage process as necessary for the development of autoimmunity. Firstly, intrauterine events associated with inflammation, as discussed above, alter the normal development of the fetal innate immune system. Secondly, during childhood the adaptive immune system, influenced by additional genetic risk factors, increases the risk of developing overt autoimmunity, which is in this case JIA. The most attractive genetic risk factor(s) to consider are in the HLA region, since strong associations have been reported there. Alteration of the developing immune system could be expressed by different mechanisms, e.g. altered thymic education of T cells as well as Th1/Th2 cytokine imbalances. Another explanation relating placental inflammation to the development of JIA in the offspring later in life would be enhanced levels of microchimerism. It has been shown that maternal microchimerism persists into adult life, suggesting a relationship between such chimerism and the development of autoimmunity [33, 40]. This maternal microchimerism might be facilitated in the presence of placental inflammation and with it the possibility of the subsequent development of autoimmunity.

The main aim of this study was to evaluate whether there were differences in reproductive fitness between mothers who have a child with JIA and mothers who have children not affected by JIA. While the primary goal was accomplished, there were limitations to the study. For instance, very early pregnancy loss may not have been noticed by the mothers and recall bias is always of concern in a retrospective study. It has been shown that women are able to remember details pertaining to pregnancies, such as recorded abortions, with 75% accuracy [41]. It is likely that early pregnancy losses and recall bias are present in the two groups (JIA mothers and control mothers) to a similar extent.

In addition, some established factors of reduced reproductive fitness were not measured. These include various factors associated with thrombophilic states, including familial homocystinaemia and mutations of coagulation factors [42]. Future studies to assess the aetiology of the increased risk of pregnancy loss in JIA mothers will have to include diligent measurements of APLA status and thrombophilia factors as well as additional environmental risk factors. Although inclusion of thrombophilic factors as such APLA in the list of confounders influencing reproductive fitness is important, we believe that the inclusion would not have changed the conclusions of this study. This is based on the observation that none of the surveyed participants reported either recurrent spontaneous abortions or recurrent thromboses, as might be expected in the presence of APLA and/or other thrombophilia syndromes, nor were any of the study participants aware of the presence of thrombophilia in their extended family. Just as SLE...
is rare in JIA families, the APLA syndrome is also uncommon among JIA patients. This is supported by the lack of recurrent thromboses or other clinical features of thrombophilia within a cohort of 700 JIA patients seen at this centre over the last two decades (M. Passo, D. J. Lovell, personal communication).

In summary, we provide initial evidence that the reproductive fitness of mothers of children with autoimmune arthropathies is impaired. Although these mothers conceive as readily as controls, they are at a higher risk of experiencing miscarriages, stillbirths and preterm delivery. Additional studies are required to ascertain more accurately the mechanisms that could account for the observed differences in reproductive fitness between JIA mothers and controls. These findings provide initial evidence for a postulated two-stage hypothesis involving the intrauterine environment as the first stage, with preconditioning of the fetus’s immune system and a second stage involving JIA susceptibility factors.

Acknowledgements

Helpful input and comments from Drs Martin Glass, Alan Jobe, Ralph Gruppo, Jerzy Stanek and Ray Bahado-Singh are much appreciated. Special thanks to Mrs Mary Kinsella for her administrative help. The study was partly supported by NIAMS T32 AR07594 and NIAMS P60 AR47784.

The authors have declared no conflicts of interest.

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