Perinatal Characteristics and Risk of Developing Primary Sjögren's Syndrome: A Case-Control Study

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ABSTRACT. ***Objective.*** To study perinatal characteristics as risk factors for developing primary Sjögren's syndrome (SS).

Methods. This was a case control study with extraction of information from birth records comprising 32 cases with SS (fulfilling the unified American-European classification criteria) and 159 controls. Cases were selected from a patient register of SS cases in Malmö, Sweden. For each case, 5 controls (living in the same catchment area, matched by date of birth, sex, and delivery unit) from the general population were identified. The relative risks of developing SS were assessed as odds ratios (OR). The primary predictor searched for was birth weight. Secondary predictors were breastfeeding during postpartum hospital stay, paternal occupation, placenta weight, gestational length, diseases during pregnancy, maternal age, parity, and history of miscarriage.

Results. Significantly increased OR were observed for high birth weight (≥ 4000 vs 3000-3999 g, OR = 3.8 95% confidence interval, CI: 1.3-11.7) and low maternal age ($p < 0.05$). Low paternal socioeconomic status (OR = 3.2, 95% CI: 1.0-10.5) and being first-born (OR = 2.5 95% CI: 1.0-5.0) tended to be associated with SS.

Conclusions. Our findings suggest that characteristics of the perinatal period may be of etiologic importance in the pathogenesis of SS. Possible mechanisms include modulation of the immune system early in life. It is conceivable that birth weight may be a marker for qualitative and/or quantitative differences in the immune system. (J Rheumatol 2005;32:665–8)

Key Indexing Terms:
SJÖGREN'S SYNDROME RISK FACTOR BIRTH WEIGHT

Primary Sjögren's syndrome (SS) is a chronic inflammatory autoimmune disease affecting 0.5% of the adult population in western countries, with a female predominance (9:1)[1]. The pathophysiology of SS is characterized by immunological disturbances of both T and B cells resulting in T cell infiltration of salivary glands and other organs and abnormal levels of autoantibodies, such as antinuclear antibodies, rheumatoid factor, and anti-Ro/SSA and anti-La/SSB antibodies[2]. The etiology of SS is largely unknown but like other inflammatory rheumatic diseases is likely to entail both genetic and environmental factors yet to be identified[3].

During the last decades perinatal risk factors have been found to be associated with subsequent development of several adult diseases such as non-insulin dependent diabetes mellitus[4,5], cardiovascular disease[5-8], atopy in children[9], and also inflammatory diseases such as inflammatory bowel disease[10] and rheumatoid arthritis (RA)[11]. In the latter it was recently reported that high birth weight, poorer socioeconomic background, and not initiating breast feeding were risk factors for subsequent development of RA[11].

We evaluated intrauterine and perinatal markers and exposures as potential risk factors for later development of SS. Our primary aim was to assess if SS is predicted by high or low birth weight. Secondary determinants included breastfeeding, length of hospital stay, paternal occupation, placental weight, gestational length, diseases during pregnancy, maternal age, parity, and previous history of miscarriage.

MATERIALS AND METHODS

Study design. This was a case-control study with 5 controls individually matched to each case.

Cases. Cases were identified from a local register in Malmö for all known patients diagnosed with SS. Individuals born between 1930 and 1981 (youngest patient in the cohort) and still living in Malmö (n = 72) were selected. From this cohort 58 cases (52 females and 6 males) fulfilled the European preliminary criteria for classification of SS[12]. Thirty-two (28 females and 4 males) also fulfilled the unified American-European classification criteria[13]. Three cases of twins were excluded from the study, since they were expected to differ substantially in many aspects, including low birth weight and higher placental weight.

Inclusion criteria for the present study were cases fulfilling the unified American-European classification criteria[13]. This classification requires (in

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contrast to the European preliminary criteria for classification of SS) the presence of pathological levels of anti-SSA or SSB antibodies or autoimmune sialoadenitis in a lower lip biopsy[13].

Using the unique personal national registration number (NRN) of each case and the nationwide multi-generation register, the NRN of the mothers of the patients with SS were identified. The birth records (stored under the mother's NRN) of each patient could then be retrieved. Following this procedure, the birth records of the 32 cases were analyzed according to a structured protocol.

Characteristics are given in Table 1.

Controls. For each case 5 consecutive control subjects born and still living in the same catchment area, matched for age, date of birth ± 5 days, sex, and delivery unit were selected using the above-mentioned population and census registers. Characteristics are given in Table 1.

Exposure. The birth records of the cases and controls underwent a structured review. For all cases and controls, the following information was extracted: birth weight and length, placental weight, breastfeeding (classified as yes if initiated), duration of hospital stay post partum (days), duration of delivery (hours), duration of pregnancy (days), parity (number of successful pregnancies and number of previous abortions or miscarriages), diseases during pregnancy, father's occupation, type of delivery (Caesarean section, vacuum extractor, forceps delivery), complications encountered during pregnancy, child's abnormality or malformation, child's weight prior to home going and APGAR score. The father's occupation was classified according to Swedish socioeconomic classification, SEI[14]. The 18 basic socioeconomic classes were merged to 2 groups: manual and nonmanual.

Information on all above mentioned variables were retrieved in > 95% of cases and controls with the exception of the APGAR score and maternal occupation. Since recording of the APGAR score only began in the early 1960s, such information was not sufficient to warrant further analyses. As the maternal occupation most often stated was housewife, it was felt that there were insufficient data to allow further analyses. Paternal occupation was missing for 17% of the cases and 15% of the controls.

Reliability testing. A blinded reliability testing of the extraction from birth records was done in 25 randomly chosen cases and controls respectively by an independent reader. Analyses revealed 98% accuracy for data extraction.

Ethics. The study was approved by the ethics research committee, Faculty of Medicine, Lund University, Sweden.

Statistics. The association between the exposures and risk of developing SS was assessed by odds ratios (OR) for categorical variables, and as p values for continuous variables. OR (with 95% confidence intervals, CI) were calculated using conditional logistic regression in SAS version 8.2. Significance values for continuous variables were calculated using linear regression with indicator terms for the matched case-control sets.

Birth weight was divided into 3 categories (< 3000, 3000-3999, and ≥ 4000 g). Large (and small, respectively) for gestational age was defined as birth weights more (or less, respectively) than 2 SD above (and below, respectively) the mean birth weight for gestational age according to the currently used Swedish reference curve[15].

Table 1. Sociodemographic and disease characteristics of cases and controls.

Variable	Cases Fulfilling the American-European Criteria for SS[13], n = 32	Controls, n = 159
Age, yrs (range)	50 (19–69)	50 (19–69)
Gender, F/M	28/4	139/20
Disease duration, yrs*, median (range)	13 (5–38)	—
Presence of autoimmune sialoadenitis, n (%)	28/30 (93)	—
Presence of anti-SSA/SSB antibodies, n (%)	18/32 (56)	—

* Since diagnosis.

RESULTS

In univariate analyses, high birth weight (≥ 4000 vs 3000-3999 g) was found in 25% of cases and 11% of controls, corresponding to an increased risk of developing SS (OR = 3.8, 95% CI: 1.3–11.7). Similarly, individuals who were born large for gestational age (LGA) had an increased point estimate for developing SS (OR = 1.8, 95% CI 0.4–7.0). Neither low birth weight nor being small for gestational age (SGA) were significantly associated with risk of developing SS (Table 2), although there was a tendency for a u-shaped relationship. Low paternal socioeconomic status tended to be associated with an increased risk of developing SS (OR = 3.2, 95% CI 1.0-10.5). In addition, SS patients had younger mothers (26.1 vs 28.3 yrs, $p < 0.05$) and tended to be more often the first liveborn child of the mother (OR = 2.5, 95% CI: 1.0–5.0). There was also an increased frequency of mentioning any disease during pregnancy by mothers of patients with SS and an associated increased risk for developing SS (Table 2). No significant association with the development of SS was observed for previous miscarriages, placental weight, or length of hospital stay post-partum (Table 2). The subgroup positive for SSA/SSB antibodies (18 of 32 cases) had similar point estimates (data not shown).

DISCUSSION

We observed that increased risk of developing SS (defined according to the American-European classification criteria) was predicted by a high birth weight and low maternal age, and tended to be associated with low paternal socioeconomic status and being the first born child of the mother.

These findings are in line with a recent study in RA that reported that high birth weight, low socioeconomic status, and not having initiated breastfeeding during the hospital stay predicted adult disease in the offspring[11]. We did not observe any significant correlation between low birth weight and SS. In contrast, low birth weight has been found to be predictive of vascular and metabolic diseases such as cardiovascular diseases, diabetes mellitus, stroke, and high blood pressure[5-9]. Our finding that being firstborn was associated with the risk for developing SS is supported by a similar finding in ankylosing spondylitis[16], although studies in this disease are conflicting[17]. To our knowledge there are no other studies addressing these issues in SS.

Our findings could have several possible pathophysiological explanations, which may include a direct involvement in the development of the immune system *in utero*, or peri- or postnatal modulation of the immune system. Our findings can also be a marker for other associated genetic or environmental risk factors.

Based on the profile of cytokines produced as part of the

Table 2. Occurrence of perinatal characteristics among 32 Swedish cases with SS according to the American-European criteria and among 159 matched controls. Data are expressed as number of exposed subjects for categorical variables and mean exposure (95% CI) for continuous variables. Relative risk expressed as univariate (OR) with 95% CI. Differences between continuous variables assessed through p values.

	Cases, n = 32	Controls, n = 159	OR (95% CI)
Socioeconomic status in father			
Manual worker	22	83	3.9 (1.1–13.4)
Non-manual worker	4	48	1.0 (reference)
Birth weight			
> 4000	8	18	3.8 (1.3–11.7)
3000–4000	18	118	1.0
< 3000	6	23	1.9 (0.6–6.0)
Large for gestational age			
Yes	3	9	1.8 (0.4–7.0)
No	28	147	1.0 (reference)
Small for gestational age			
Yes	1	11	0.4 (0.0–3.5)
No	30	145	1.0 (reference)
Breast feeding commenced during the postnatal hospital stay			
Yes	2	12	1.0 (0.2–5.0)
No	28	142	1.0 (reference)
Maternal diseases during pregnancy*			
Yes	6	15	3.9 (0.9–16.9)
No	26	144	1.0 (reference)
Maternal diseases before pregnancy*			
Yes	7	26	1.5 (0.6–3.7)
No	25	133	1.0 (reference)
Being first born in the sibship			
Yes	21	73	2.7 (1.1–6.8)
No	11	86	1.0 (reference)
Previous miscarriages in mother			
Yes	5	26	0.9 (0.3–2.8)
No	27	131	1.0 (reference)
Mean placental weight, g	641 (595–689)	608 (587–629)	p = 0.199
Mean maternal age at delivery, yrs	26.1 (24.1–28.0)	28.3 (27.4–29.2)	p = 0.044
Mean gestational length, days	286 (277–295)	279 (275–283)	p = 0.138
Mean hospital stay post-partum, days	7.9 (6.9–9.0)	7.7 (7.2–8.1)	p = 0.61

* Any recorded intercurrent diseases in the records.

inflammatory response, the immune response can be characterized as either a Th1 or Th2 response. The Th1 part of the immune response is characterized by a cell mediated immune response and the Th2 by a humoral response[18]. The normal immune system develops from a predominance of a Th2-type response at birth to a Th1-type response in early childhood[19-22]. Absence of this shift has been associated with increased risks of developing atopy[19,22]. RA and SS are at the site of inflammation characterized by a predominance of the Th1 response[2,18]. In analogy with our current understanding of the development of atopy, it is possible that the early balance of Th1 and Th2 response may also affect the risk of adult autoimmune diseases such as SS and RA, or determine their natural course. Against this background, it is conceivable that our findings may be a marker for qualitative differences in the immune system. Alternatively, birth weight may simply reflect a quantitative difference with a larger number of immune-competent cells in subjects with high birth weight.

A few strengths and limitations of our study should be mentioned. The cases were recruited from the local register (started in 1984) that has been estimated to contain at least one-third of the prevalent cases in the catchments area[23], based on the reported prevalence of 0.5%[1,24]. Hence, some selection bias towards more severe cases is likely. On the other hand a prevalence of 0.5% is based on population studies[1,24] using proposed classification criteria[12,13] that identified subjects fulfilling criteria but who were unaware of having SS and were undiagnosed. Hence this figure may be an overestimation of the true disease prevalence. Moreover, although we identified prevalent rather than incident cases with SS, the cases were too young to allow for substantial bias due to selective survival from SS. Furthermore, increased mortality in SS has only been seen in small subgroups and there does not appear to be an overall increase in mortality in SS[23].

Controls were selected and matched for age, sex, date, and place of birth, independent of their risk of developing SS, and are likely to represent the exposure distribution in the general population.

The risk of recall or information bias was minimized as exposure information was recorded prior to the occurrence of the outcome, and because the exposure information was collected using a structured process independent of the outcome status. Furthermore, reliability testing for data extraction from the birth records did not reveal any major misreading.

In conclusion, we found that high birth weight and younger maternal age were linked with increased risk of developing SS in mid-life. Our findings suggest that characteristics of the perinatal period may be of etiologic importance in the pathogenesis of SS. From these data it is not possible to draw any firm conclusion regarding any effects of perinatal exposures on the SS phenotype or prognosis.

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