Background: Group B meningococcal (GBM) disease induces antibodies that react in vitro with neural cell adhesion molecules in fetal brain tissue. Because IgG antibodies to GBM cross the placenta, the authors investigated whether women with a previous GBM disease had an increased risk of giving birth to preterm or to stillborn infants and whether the live-born children had an increased risk of birth defects.

Methods: Data were obtained from 4 national registries in the period 1974–2005 to form 2 cohorts: (1) 1422 women with confirmed GBM disease, and (2) their 502 firstborn children.

Results: Overall, there was no increased risk of preterm or stillbirths among the first cohort. Among the children, there was no increased risk of being born small for the gestational age, having birth defects (OR: 1.00; 95% CI: 0.53–1.90), diseases of the nervous system (HR: 0.38; 95% CI: 0.08–1.74), or any diseases within the first 3 years of life (HR: 1.06; 95% CI: 0.78–1.45) compared to births from a reference population with prior group C meningococcal disease.

Conclusions: The results do not support the proposal that GBM is associated with immunoreactive disease that may affect the health of the offspring and are consistent with previous findings that GBM disease is not associated with an increased risk of autoimmune disease.

Key Words: meningococcal disease, Neisseria meningitidis, birth defects, congenital malformations, PSA, NCAM, epidemiology, Denmark

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Efforts to investigate a polysaccharide-based group B Neisseria meningitidis (GBM) vaccine have been hampered for 2 main reasons: the poor immunogenicity of the capsular polysaccharide alone and concerns about potential autoimmunity induced by anti-bodies toward the capsular polysaccharide, polymers of \(\alpha(2\rightarrow8)\) linked N-acetylneuraminic acids (PSA), present in the GBM capsule that is structurally identical to PSA present on neural cell adhesion molecules (PSA-NCAM) in fetal and adult mammalian neural tissues. After birth, the relatively long chains of PSA on NCAM (>12 residues), which are more reactive with PSA antibodies than shorter chains, become progressively shorter in most human tissues, except in certain brain tissues and on natural killer cells, presumably changing their NCAM-function from a plasticity promoting to a more stability promoting molecule.

Convalescent patients from GBM disease have increased concentrations of immunoglobulin M and immunoglobulin G PSA antibodies. Immunoglobulin G, but not immunoglobulin M, crosses the placenta. Devi et al have reported equal or higher PSA antibody levels in the umbilical cord than in the corresponding maternal sera. PSA antibodies are common in the general population, likely arising from intestinal carriage of Escherichia coli K1, asymptomatic pharyngeal carriage of nonpathogenic GBM, or exposure to Moraxella nonliquefaciens, all expressing capsular PSA. Because group C N. meningitidis (GCM) capsular polysaccharide, polymers of \(\alpha(2\rightarrow9)\) linked N-acetylneuraminic acids, differs from GBM capsular polysaccharide by only 1 linkage, convalescent patients from GCM disease can serve as a control group in addition to the background population. The capsular polysaccharides of GBM and GCM do not cross-react immunologically.

In a Danish national cohort study, we found that subjects convalescent from GBM disease had no increased risk of autoimmune diseases up to 31 years after their acute episode of meningococcal disease compared to persons with a history of GCM disease or persons without a history of meningococcal disease. We formed the following null hypotheses to explore whether GBM disease induces an immunologic reaction in the fetus:

Women convalescent from GBM disease have the same risk of preterm delivery, giving birth to stillborn infants or infants small for the gestational age as women with a history of GCM disease or women with no history of meningococcal disease, and children born to women with a history of GBM disease have the same risk of birth defects and/or diseases within the first 3 years of life as children born to women with a history of GCM disease or women with no history of meningococcal disease.

MATERIALS AND METHODS

The study was based on 4 national registries: The Danish Civil Registration System, the Registry of Communicable Diseases, the Hospital Discharge Registry and the National Registry of Abortions. The study was approved by the Danish Data Protection Agency and person-related information was stored and treated in accordance with regulations. Thus, no informed patient consent was required.

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since 1974.21

The Registry of Communicable Diseases. Since 1980, it has been mandatory for clinicians to report specified cases of communicable diseases, including meningococcal disease, to the Department of Epidemiology at the Statens Serum Institut.20 In addition, the Neisseria and Streptococcus reference laboratory, also at Statens Serum Institut, has received meningococcal disease isolates for serogrouping from the local Departments of Clinical Microbiology since 1974.21

Copies of laboratory results have since 1992 been sent concurrently to the Department of Epidemiology and a notification form was requested if not received.21,22

In a capture-recapture analysis, the completeness of the database from 1994 to 2002 has been estimated to be above 95%.23,24 The completeness of the notifications for meningococcal disease in the period 1974–1992 in Denmark is estimated to be high because of the severity of the disease and because monitoring of invasive meningococcal strains by serogroup, only done at Statens Serum Institut, was considered important, owing to the availability of the polysaccharide group A and C meningococcal vaccines from the beginning of the 1970s.18,21 We used data from the entire period 1974–2005 for this study.18

The Hospital Discharge Registry. The hospital discharge registry has recorded all diagnoses of hospital discharges in Denmark, including diagnoses from obstetric and pediatric departments. Birth defects have been registered centrally since 1963 but computerized only since 1973. Birth defects have been recorded concurrently in independent registries: the National Registry of Congenital Abnormalities (1983–1995),25 the Medical Birth Registry (1973-present),26 and the Hospital Discharge Registry (1977-present).27 Larsen et al28 compared the 3 registries for birth defects in the period 1991–94. The Hospital Discharge Registry had a predictive value of birth defects of 88.2% (95% confidence interval (CI): 85.9–90.5%) and completeness of 89.9% (95% CI: 87.7–92.1%), which they concluded was acceptable for general surveillance and epidemiologic research regarding birth defects. The completeness of the Hospital Discharge Registry on birth defects for the period 1977–1991 has to our knowledge not been accessed, but we consider the risk for differential misclassification small, because a history of meningococcal disease in the mother is not an established risk factor for birth defects in the offspring. The 2 other registries had higher predictive values, but their completeness was calculated to be below 40%. We decided to use data from the Hospital Discharge Registry for the period 1974–2005.

Birth defects have the following codes in the eighth revision of the International Classification of Diseases (ICD-8) 740.00–759.99 and in ICD-10 Q00.0–Q99.9. We excluded the following diagnoses (ICD-8; ICD-10): patent ductus arteriosus (747.07; Q52.0), undescended testis (752.10–752.19; Q53.00–Q53.99) and hip dislocation (755.60–755.69; Q65.00–Q65.99) because the diagnostic criteria of outcomes. In the subgroups may add up to more than the overall number sum of outcomes. The median time between GBM disease and the “outcome variable” was 13.5 years (10% quantile and 90% quantile: 5.6–23.4 years) and 15.0 years (10% quantile and 90% quantile: 6.4–24.9 years) for GMC disease.

RESULTS

The median time between GBM disease and the “outcome variables” was 13.5 years (10% quantile and 90% quantile: 5.6–23.4 years) and 15.0 years (10% quantile and 90% quantile: 6.4–24.9 years) for GMC disease.

Pregnancy and Delivery. Cohort I included 1422 females with previous GBM disease, 506 with previous GMC disease, and Danish females without known GBM or GMC disease as referents. Among
Among the 502 children born to women with a previous GBM disease, we identified 41 children with birth defects (Table 2, http://links.lww.com/A615). The comorbidity adjusted odds ratio was 3.89 (95% CI: 1.11–13.63). The results were based on 5 cases only, which were (ICD-8/ICD-10): iron deficiency anemia (280.09); hemorrhagic thrombocytopenia (287.29); hereditary factor VIII deficiency (2 subjects, D66.9) and nutritional anemia, unspecified (D53.9). No cases were registered in this subgroup among children born to mothers with a history of GCM disease (Table 3, http://links.lww.com/A615).

We found no increased risk of neurodevelopmental disorders within the first 3 years of life. Differences between the groups for mental and behavioral disorders (HRcomorbidity adjusted: 0.53; 95% CI: 0.14–1.96), and diseases of the nervous system (HRcomorbidity adjusted: 1.07; 95% CI: 0.45–2.53), were insignificant (Table 3, http://links.lww.com/A615).

**DISCUSSION**

We studied women with previous GBM disease to clarify if they had increased risk of late pregnancy complications and/or their biologic children had increased risk of adverse birth outcomes. Overall, we did not find an association between females’ previous GBM disease and stillbirths, preterm delivery, birth of infants small for the gestational age, and birth defects or diseases in the children’s first 3 years of life.

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**TABLE 1.** Odds Ratio (OR) for Selected Pregnancy Outcomes for Females With Previous Meningococcal Disease Group B or Group C Disease Compared to the Background Population and the Group B/Group C Ratio

<table>
<thead>
<tr>
<th>Pregnancy Outcome</th>
<th>Group B OR (95% CI)</th>
<th>Group C OR (95% CI)</th>
<th>B/C Ratio OR (95% CI)</th>
<th>Background Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stillbirth?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted*</td>
<td>0.79 (0.11–5.65)</td>
<td>2.09 (0.29–14.99)</td>
<td>0.38 (0.02–6.12)</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>0.78 (0.11–5.53)</td>
<td>2.05 (0.28–14.70)</td>
<td>0.38 (0.02–6.13)</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>1</td>
<td>1</td>
<td>4811</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>227</td>
<td>86</td>
<td>846,816</td>
</tr>
<tr>
<td>Delivery before gestational wk 37?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted*</td>
<td>0.95 (0.53–1.71)</td>
<td>0.83 (0.30–2.25)</td>
<td>1.16 (0.36–3.70)</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>0.96 (0.54–1.73)</td>
<td>0.83 (0.31–2.27)</td>
<td>1.15 (0.36–3.68)</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>12</td>
<td>4</td>
<td>45,773</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>213</td>
<td>82</td>
<td>775,290</td>
</tr>
<tr>
<td>Infant weight at delivery below 2500 g?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted*</td>
<td>0.66 (0.27–1.61)</td>
<td>1.05 (0.33–3.34)</td>
<td>0.82 (0.15–2.66)</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>0.65 (0.27–1.57)</td>
<td>1.04 (0.33–3.29)</td>
<td>0.83 (0.15–2.68)</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>5</td>
<td>3</td>
<td>28,383</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>222</td>
<td>83</td>
<td>816,944</td>
</tr>
<tr>
<td>Small for gestational age at delivery?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted*</td>
<td>0.64 (0.39–1.04)</td>
<td>0.68 (0.32–1.48)</td>
<td>0.94 (0.38–2.36)</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>0.64 (0.39–1.04)</td>
<td>0.69 (0.32–1.50)</td>
<td>0.92 (0.37–2.31)</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>17</td>
<td>7</td>
<td>63,299</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>208</td>
<td>79</td>
<td>493,534</td>
</tr>
</tbody>
</table>

*Adjusted for age, calendar period, county of residence, and sex of the infant.

For 2 live-born infants records of gestational age at birth were unavailable.
GBM and GCM convalescents were compared with the entire Danish population of women with no history of meningococcal disease. Because meningococcal disease involves either systemic or CNS inflammation, a high proportion of survivors (11–19%) have sequelae, and more so when neurodevelopmental outcomes are considered (ie, learning difficulties and social problems).31–37 GCM is second to GBM in the developed world as disease-causing N. meningitidis serogroups.38

Few countries have health registries that allow longitudinal follow-up and comparison of women with respect to pregnancy delivery outcomes and complications in their offspring where information is collected independently of the study questions. However, the study design has some limitations because we relied on recorded data (ie, the inability to ask for specific detailed information, like waiting time to pregnancy, number of spontaneous abortions, and milder childhood diseases that do not demand hospitalization). In addition, disease coding has changed over time and only limited quality control of the registered codes has been conducted for the various outcomes. The results, however, are adjusted for calendar time with regard to the pregnancy outcomes and matched for the analyses of birth defects and diseases within the first 3 years of life.27 It is likely that women with a history of a severe meningococcal disease are more prone to hospitalization afterward than is the background population. However, such a differential misclassification would only overestimate the burden of disease-complication in the study group compared to the background population, and we do not expect persons with a GBM disease to differentiate from women with a history of GCM disease. In addition, the median time between meningococcal disease and pregnancy outcomes and birth defects was >10 years, which minimizes risk of diagnostic dependency between exposure and outcome events.

The registered data on abortions were limited to induced abortions for the period 1977–2005 and spontaneous abortions at hospitals since 1995. In the initial analyses, we studied abortions as an outcome but did not find an association with persons with a history of GBM disease. Thus, we have refrained from reporting results on abortions for 2 reasons: first, a reason for an induced abortion may have other explanatory factors, like social or disease-related causes and because we do not have this information, we are unable to control for it and may risk reporting a biased result. Second, information on spontaneous abortions are sparse, only to be reported from hospitals since 1995. Because most abortions are spontaneous and occur outside hospitals setting and probably often without the women knowing it, we are left without the number of pregnancies in Denmark. Accordingly, we could not assess any association of neuronal malformations, which might occur in the first trimester when the central nervous system and most organs are initiated. However, according to our study, if neuromalformations do occur without inducing an abortion, they are not associated with preterm delivery, giving birth to an infant small for gestational age, birth defects in offspring, or diseases within the first 3 years of life according to our study.

Because advanced screening programs of pregnant women have only been instituted recently in Denmark, any subsequent decrease in birth defects should have little impact on the 2 cohorts covering 28 years each.

With the exception of the group of urinary tract defects, we found no increased risk of birth defects in children born to women with a history of GBM disease compared to the general reference population. Within the group of birth defects of the urinary system only congenital hydrenephrosis was registered in more than 1 subject in each of the 3 exposure groups; the diagnosis was not made significantly more often in children born to mothers with a history of GBM disease compared to the reference populations.

We demonstrated previously that persons with a history of GBM disease are at no increased risk of autoimmune diseases for up to 31 years after meningococcal disease.15 If PSA antibodies react as autoantibodies, binding to PSA-NCAM expressed particularly in the fetal tissue, we would have expected the persons with a history of GBM disease to be at increased risk of autoimmune diseases and in particular, the fetuses of the exposed mothers to be vulnerable to neurological complications and birth defects.

The lack of information on pre- and early pregnancy complications, including waiting time to pregnancy and spontaneous abortions preclude conclusions for the early pregnancy period. However, for the period around delivery and the first 3 years of life, our data indicate no statistically significant associations between previous GBM disease and developmental abnormalities during ontogenesis which persist until birth. These results are consistent with our findings that persons with a history of GBM disease have no increased risk of autoimmune diseases later in life.

REFERENCES