Archival Report

Biological Psychiatry

Hypothyroxinemia During Gestation and Offspring Schizophrenia in a National Birth Cohort

David Gyllenberg, Andre Sourander, Heljä-Marja Surcel, Susanna Hinkka-Yli-Salomäki, Ian W. McKeague, and Alan S. Brown

ABSTRACT

BACKGROUND: Evidence from animal and human studies indicates that thyroid hormone deficiency during early gestation alters brain development. As schizophrenia is associated with prenatal brain insults and premorbid cognitive deficits, we tested the a priori hypothesis that serologically defined maternal thyroid deficiency during early gestation to mid-gestation is associated with schizophrenia in offspring.

METHODS: The investigation is based on the Finnish Prenatal Study of Schizophrenia, a nested case-control study that included archived maternal sera from virtually all pregnancies since 1983 (N = >1 million). We identified all offspring in the cohort with a diagnosis of schizophrenia based on the national inpatient and outpatient register and matched them on sex, date of birth, and residence in Finland at time of onset of the case to comparison subjects (1:1) from the cohort. Maternal sera of 1010 case-control pairs were assessed for free thyroxine, and sera of 948 case-control pairs were assessed for thyroid-stimulating hormone.

RESULTS: Maternal hypothyroxinemia (free thyroxine ≤10th percentile, normal thyroid-stimulating hormone) was associated with an increased odds of schizophrenia (odds ratio = 1.75, 95% confidence interval = 1.22–2.50, p = .002). When adjusted for maternal psychiatric history, province of birth, and maternal smoking during pregnancy, the association remained significant (odds ratio = 1.70, 95% confidence interval = 1.13–2.55, p = .010).

CONCLUSIONS: In a large, national birth cohort, prospectively documented hypothyroxinemia during early gestation to mid-gestation was associated with increased odds of schizophrenia in offspring. This information can inform translational studies of maternal hypothyroxinemia examining molecular and cellular deviations relevant to schizophrenia.

Keywords: Biomarker, Cohort, Neurodevelopment, Prenatal, Schizophrenia, Thyroid

http://dx.doi.org/10.1016/j.biopsych.2015.06.014

Exposure to low thyroid hormone levels in utero alters brain development of offspring in both animal models and humans (1–3). Experimental rodent studies have shown that maternal thyroxine deficiency, even in the mild range, causes aberrant prenatal neurodevelopment (1–3). One such outcome, based on studies of rat dams, is abnormal distribution of neurons in the hippocampus; this can be prevented by replacement of maternal thyroxine in early pregnancy (4).

In humans, the fetus is completely dependent on maternal thyroxine during early gestation, as fetal thyroxine production begins during gestational weeks 12–14 (5). Maternal thyroxine crosses the placenta, and fetal thyroxine correlates well with maternal thyroxine (6). Clinical hypothyroidism during pregnancy is an established risk factor for cognitive dysfunction of offspring (7) and neuroanatomic abnormalities including reduced hippocampal volume (8). Low maternal free thyroxine (fT4) in the absence of clinical hypothyroidism is termed hypothyroxinemia and defined as fT4 below the 10th percentile with normal levels of thyroid-stimulating hormone (TSH). An emerging literature has yielded intriguing evidence that hypothyroxinemia is also associated with delayed cognitive, motor (9–11), and speech development in offspring (11). Because schizophrenia is associated with disrupted prenatal neurodevelopment and impaired cognitive function (12), we tested the hypothesis that maternal hypothyroxinemia and low, continuously defined maternal fT4 levels during early gestation to mid-gestation are associated with schizophrenia in offspring. In an additional analysis we examined whether schizophrenia in offspring is associated with maternal hypothyroidism and with other maternal clinical thyroid disorders (see Laboratory Assays and Classification of Thyroid Disorders in Methods and Materials for definitions).

METHODS AND MATERIALS

The investigation was based on the Finnish Prenatal Study of Schizophrenia (FiPS-S), which used a nested case-control design (13). The sampling frame was defined so that the members of the birth cohort were within the age of risk for schizophrenia. Nationwide registers were used to identify

SEE COMMENTARY ON PAGE 950

 ISSN: 0006-3223

cases born between 1983 (the first birth year of the cohort) and 1998 and diagnosed with schizophrenia or schizoaffective disorder before December 31, 2009 (see Case and Control Identification). The maximum age was 26 years.

Description of Cohort and Biobank

All subjects in FiPS-S were derived from the Finnish Maternity Cohort (FMC). The FMC consisted of all offspring with archived maternal sera drawn during pregnancy in Finland since 1983 (N = >1 million). Sera were drawn during the first trimester or the early second trimester (5th–95th percentile = months 2–4 of pregnancy) from >98% of the gravidae, following informed consent, for screening of human immunodeficiency virus, syphilis, and hepatitis. One maternal serum sample was obtained for each pregnancy. After the screening, the remainder of each sample was stored as 1 aliquot at −25°C in a single, centralized biorepository (National Institute of Health and Welfare). All of the serum samples in the FMC can be linked with offspring by the unique personal identification number that has been assigned to all residents of Finland by the Finnish Population Registry since 1971. The personal identification numbers of the mothers of case subjects and matched control subjects were linked to the FMC sera biobank and to other registers discussed subsequently.

Finnish Population Register

The computerized nationwide Finnish Population Register was established in 1971. It includes comprehensive data on place of birth, twinning, date of emigration, date of death, and biological parents, including their dates of births.

Case and Control Identification

The Finnish Hospital and Outpatient Discharge Register (FHDR), maintained by the National Institute of Health and Welfare, was used to identify all recorded diagnoses for psychiatric hospital admissions and psychiatric outpatient treatment visits among members of the FMC. The FHDR was established in 1963, and computerized data are available from 1987 to the present. The register contains the personal and hospital identification codes and primary and secondary psychiatric diagnoses.

To identify the cases for the present study, we linked the FMC and the FHDR. All cases with schizophrenia (ICD-10 F20) or schizoaffective disorder (ICD-10 F25) in the FHDR were identified. Hereinafter schizophrenia and schizoaffective disorder are referred to as schizophrenia. The age at first treatment was recorded by the first contact with a psychiatric facility with a diagnosis of schizophrenia. The diagnostic validity of schizophrenia in the FHDR was very good; in a previous study, 93% of subjects with a diagnosis of schizophrenia in the FHDR were assigned a consensus diagnosis of schizophrenia (14). The total number of schizophrenia cases was 1514 (13). A sufficient amount of maternal sera was available in the study to measure fT4 on 1010 case-control pairs and TSH on 948 pairs; 903 pairs were assayed for both fT4 and TSH. The schizophrenia cases were matched 1:1 to control subjects drawn from the FMC without schizophrenia, other nonaffective psychotic disorders, or bipolar disorder on the date of birth (± 1 month) for sex and residency of Finland at the time of case diagnosis. The control subjects for the study were randomly drawn from all control subjects fulfilling these criteria because there were many control subjects with all of these characteristics.

Laboratory Assays and Classification of Thyroid Disorders

Measurements of maternal fT4 and TSH were performed blind to case/control status using chemiluminescent microparticle immunoassays with the Architect i2000 automatic analyzer (Abbott Diagnostics, Abbott Park, Illinois). The lower limits of detection for fT4 and TSH were 5.1 pmol/L and .0025 mIU/L, respectively. The intra-assay and interassay variation were 3.6% and 7.8% for fT4 and 1.7% and 5.3% for TSH, respectively.

To facilitate the clinical interpretation of the data, we conducted additional analyses of maternal serologically defined thyroid disorders in relation to schizophrenia. Given that fT4 varies during pregnancy (15,16), the lack of trimester-specific reference values from the manufacturer, and the fact that the sera had been frozen and stored for up to several years (17), we defined the cutoff points to categorize these groups based on percentiles in the control population. Maternal hypothyroxinemia was classified as fT4 ≤10th percentile and TSH >5th–95th percentile, consistent with percentiles used in clinical guidelines for thyroid disorders (15) and other thyroid studies (9,11). In a sensitivity analysis, we used an alternative cutoff point to define hypothyroxinemia—fT4 ≤5th percentile and TSH >5th–95th percentile. The cutoff points for the other maternal clinical thyroid disorders were also consistent with a general population subsample of the current biobank (16). Hypothyroidism was defined as fT4 ≤5th percentile and TSH >95th percentile; subclinical hypothyroidism, as fT4 >5th–95th percentile and TSH >95th percentile; hyperthyroidism, as fT4 >95th percentile and TSH ≤5th percentile; and subclinical hyperthyroidism, as fT4 >5th–95th percentile and TSH ≤5th percentile. Table 1 lists the cutoff values for fT4 in pmol/L and for TSH in mIU/L.

Covariates

The covariates in the study were selected based on the literature on schizophrenia (18–20) and outcomes of maternal thyroid hormone disorders (9–11,21–25). These included maternal educational level; previous births; maternal age; maternal history of schizophrenia, affective disorders, or any psychiatric disorder; urbanicity of birth; birth province; twinning; and the gestational week of blood draw (classification shown in Table 2). Gestational week of the blood draw was obtained from the FMC, whereas all other covariates were derived from the Finnish Population Register. The degree of urbanization of the birth municipalities was classified based on national standards used by Statistics Finland (26): a densely populated area was defined as a 250 m^2 area with >200 inhabitants. Municipalities with ≥90% of the population living in densely populated areas were classified as urban; with 60%–89%, as semiurban; and with <60%, as rural. Urbanicity and province of birth were highly correlated in control subjects (χ^2 = 134.7, df = 6, p < .0001), and 50.8% of the controls born in Southern Finland were born in an urban area