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Early prenatal exposure to pandemic influenza A (H1N1) infection and child psychomotor development at 6 months – A population-based cohort study

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ABSTRACT

Background: Studies investigating gestational influenza and child neurodevelopment are still scarce, particularly concerning timing of infection in pregnancy. This is the first study to investigate associations between gestational influenza and infant psychomotor development and temperament at 6 months.

Methods: Data from The Norwegian Influenza Pregnancy Cohort, established during the 2009 swine flu pandemic, were utilized. Information on influenza infection, vaccination, maternal health and child health and development is available from questionnaires, national registry data and maternal blood samples drawn at delivery. Maternal influenza A H1N1 pdm09 infection was serologically confirmed. 609 children with complete data were identified. Children of exposed and non-exposed mothers were compared using generalized linear models.

Results: Children exposed to influenza during gestational weeks (gw) 0–8 had adjusted general development scores indicating slightly delayed development compared to non-exposed children (0.28 standard deviations (SD) 95% confidence interval (CI): −0. 01; 0.58; p = 0.06). The temperamental scores of children exposed during gw 0–8 were slightly higher (0.31 SD; 95% CI: −0. 03; 0.64; p = 0.07) than non-exposed children indicating a more difficult temperament. In comparison, the developmental scores for children exposed in gw 9–40 were −0.31 SD (95% CI: −0. 65; 0.04; p = 0.09) better than non-exposed children, while the temperamental scores were 0.17 (95% CI: −0. 23; 0.56; p = 0.36) for the same period.

Conclusion: Modest associations were found between maternal influenza A (H1N1) pdm infection during gestational weeks 0–8 and psychomotor development at 6 months.

1. Background

Previous research indicates that prenatal virus infections may adversely affect fetal neurodevelopment [1]. Epidemiological studies from previous influenza pandemics have shown that prenatal exposure to influenza is associated with lower educational attainment and lower IQ scores in offspring, unemployment, increased risks of autism, major affective disorders, psychoses and mental retardation [2–7]. Moreover, evidence from epidemiological and clinical investigations suggests that prenatal influenza infection is a notable environmental risk factor in the etiology of schizophrenia [1], although findings are inconsistent [8].

A systematic review of prenatal infection and neurodevelopment indicates that influenza exposure during early pregnancy may be more harmful than later exposure [9]. Previous epidemiological studies on gestational infection and schizophrenia found 2nd trimester to be a critical time window for infection [10]. However, a review of more recent research using more reliable methodology, indicates that infection during the earliest weeks of gestation may be particularly harmful [11]. Findings from epidemiological studies have further been corroborated in a large number of animal studies, where maternal immune activation (MIA) induced by use of a viral infection mimic (polyinosic: polycytidylic acid (poly I:C)), resulted in short- or long-term

Abbreviations: Norflu, Norwegian Influenza Pregnancy Cohort Study; ICQ, Infant Characteristics Questionnaire; ASQ, Ages and Stages Questionnaire; ICD, International Classification of Diseases; ICPC, International Classification of Primary Care; HI titer, hemagglutination-inhibition antibody titer; ILI, influenza-like illness; SCL, symptom check list; gw, gestational week; GA, gestational age; LMP, last menstrual period

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neurodevelopmental abnormalities in the offspring [12–14].

Pregnant women are particularly susceptible to influenza infection and at increased risk of severe disease due to physiological changes in the cardiovascular, respiratory and immune systems [15,16]. Maternal influenza infection in pregnancy is also associated with increased risk of adverse pregnancy outcomes [17,18]. However, to the authors' knowledge no studies have so far investigated the potential associations between serologically confirmed maternal influenza A (H1N1) pdm09 virus infection (hereafter H1N1) in pregnancy and infant neurodevelopment. Thus, the aim of the current study was to investigate temperament and psychomotor development among 6-month-old children exposed to pandemic influenza H1N1 infection in utero, compared to non-exposed children.

2. Methods

2.1. Data sources and study population

The Norwegian Influenza Pregnancy Cohort Study (NorFlu) was established by the Norwegian Institute of Public Health during the 2009 influenza A(H1N1) pandemic. According to national surveillance data, the main pandemic wave occurred in Norway between Oct. 1st and Dec. 31st [19]. Enrollment of pregnant women to NorFlu started in February 2010. Women with lmp between June 1st 2009 and Dec. 31st 2009, and thus pregnant during the pandemic were recruited from four hospitals in the Bergen- and Oslo-area at the time of their routine ultrasound around pregnancy week 17–18. In addition, a few women were recruited at the time of delivery. All babies were delivered by September 25th 2010. See Fig. 1 for information on the sample. Of the 5332 invited mothers, 3203 (60.0%) consented to participate. Of these, 609 unvaccinated mothers with complete exposure and outcome data were included in the analyses. Information about mothers and babies was obtained from self-administered questionnaires during pregnancy and 6 months after pregnancy, from maternal blood samples collected at delivery, and national registers (for more details about the data collection, see eMethods in Supplement).

2.2. Outcomes

2.2.1. Fussy baby scale - the Infant Characteristics Questionnaire

Ten items from the Infant Characteristics Questionnaire (ICQ 6-mo.) [20] were used to measure temperament among the babies. The Fussy baby scale is one of four subscales of the ICQ that has been identified through principal component analysis and has been found to be the most clear-cut and valid factor of the ICQ 6-mo. [20]. The scale is detailed in eMethods in Supplement. Cronbach's alpha for the scale was 0.77. The scale was positively skewed and hence logarithmically transformed (ln) to approximate a normal distribution, and standardized. Higher scores indicate more difficult temper.

2.2.2. Psychomotor development - the Ages and Stages Questionnaire

General psychomotor development among the children was measured by the validated full-scale 30 item 6 months version of the Ages and Stages Questionnaire (ASQ) [21–23]. The ASQ consists of five subdomains with six items each, namely: gross motor, fine motor, problem solving, personal/social, and communication. The total score was used as main outcome, although sub-analyses were run on each of the five factors as well. Higher scores indicate delayed development. The ASQ total and each sub-domain were highly positively skewed and logarithmically transformed (ln) to approximate a normal distribution. Each domain-score and the ASQ total were standardized after the item scores were summed. Cronbach's alpha of the ASQ total was 0.78. For additional information, see eMethods in Supplement.

2.3. Exposures

Maternal influenza infection was defined according to maternal reports of gestational influenza-like illness (ILI) within the past 12 months and laboratory confirmed influenza A (H1N1) pdm09. Most participants were pregnant in the first or second trimester during the peak pandemic period (Oct.–Dec. 2009).

Almost one third (N = 27) of the seropositive women reporting ILI also had a primary care physician contact leading to a clinical diagnosis of influenza according to the International Classification of Primary Care, Second Edition (ICPC-2), code R80 [24]. The proportion of women with low (≥10–40) and high HI antibody titers (≥40) was almost equal for both influenza recorded in the registers and self-reported ILI. Therefore, sera with HI titer values ≥ 10 were considered seropositive.

Four main exposure groups were ultimately defined: 1) seropositive women with reported ILI, 2) seropositive women with no reported ILI, 3) seronegative women with reported ILI, and 4) seronegative women with no report of ILI (non-exposed).

Based on the assumption that influenza in early pregnancy (during the embryogenesis) may be more harmful to the fetus than later exposure, we explored the impact of timing of exposure according to gestational length for exposure groups 1 and 3 reporting influenza-like symptoms (see Design and analyses). Due to the study design and sampling period relative to the pandemic peak in Norway, very few participants had been exposed to influenza in the third trimester.

2.4. Covariates

Information on potential confounders was obtained from the Medical Birth Registry of Norway, including; maternal age, parental education, mother's marital status, parity, pregnancy length, preeclampsia, maternal smoking and alcohol use during pregnancy as well as several maternal somatic conditions, including; diabetes, thyroidea, epilepsy, asthma, kidney disease and heart disease. Information on somatic diseases is based on check boxes completed by doctor/midwife or additional written information recoded into International Classification of Diseases 10th Revision (ICD-10) codes. Sensitivity analyses were performed with and without gestational length as covariate, as this might be in the causal pathway between influenza exposure and outcome. Information on maternal psychological distress at 6 months (Hopkin's Symptom Check List (SCL-8)), native language and child's age at completion of the questionnaire was obtained from the pregnancy questionnaires and the 6 months questionnaire. Additional covariates (nutritional variables, birth complications etc.) were tested in a reduced sample, see eMethods in Supplement. Choice of covariates was based on literature review and considerations of factors that could be plausible confounders [25–28].

2.5. Design and analyses

A linear multivariate model was specified, using the Generalized Linear Model (GLM) procedure (SPSS 22.0, GENLIN) to investigate the impact of gestational influenza exposure on the psychomotor development and temperament scores of the offspring adjusting for the previously mentioned covariates. The scores in children of mothers with influenza in pregnancy were compared to the scores in children of mothers without influenza in pregnancy. Crude and fully adjusted associations are presented as regression coefficients (B) with 95% confidence interval (CI). The coefficients show mean deviations from children of unexposed mothers in fractions of a standard deviation. We explored the following models two models:

1) Main model; timing of influenza categorized into exposed < gestational day 0, reported exposure gw 0–8 and gw 9–40 (seropositive and seronegative groups, respectively), and HI positive but