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 S.D (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, .

*Key words:* influenza, pandemic, prenatal, neurodevelopment, temperament, H1N1

*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

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 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.

1. **Methods**
   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- 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**).

(Fig. 1)

* 1. *Outcomes* 
     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.

* + 1. *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 sub-domains 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**.

* 1. *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.

* 1. *Covariates*
  2. 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] *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 presentedas 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 no reported influenza-like illness (subclinically ill).
2. Supplementary model; exposed <gestational day 0, reported exposure any time in pregnancy (seropositive and seronegative groups) and subclinically ill.

For all models, the overall effect of exposure to influenza was tested - providing an overall p-value for the whole predictor variable. Separate p-values are also provided for the subgroups.

Sensitivity analyses were performed, testing the effect of influenza exposure according to pregnancy trimester, and also for exposure ‘any time’ in pregnancy. These results are briefly described in text.

* 1. *Ethics*

The study was approved by the Regional Committee for Medical and Health Research Ethics in South-Eastern Norway (ref no 2009/2165). Informed consent was obtained from all individual participants included in the study.

1. **Results**
   1. *Descriptives*

No major differences between the total unvaccinated sample and the study sample were found (see Tables 1-2). The differences between the study sample and the original sample for the variables not presented in Tables 1-2, were as follows; The current sample were virtually identical to the original sample for the share being married/cohabitants; 96.4 % vs 97.2 %, and for the share having Norwegian as their first language; 87.2 % vs 90.0 %. Maternal education ranged from 9 years of mandatory schooling to > 4 years at university, with 81.8 % having university education as compared to 67.8 % in the original sample. The corresponding numbers for paternal education were; 81.8 % in our sample vs 82.2 % in the original sample. Almost 2 % were smoking sometimes/daily in both samples . Alcohol consumption was virtually identical in the two samples; about 8 % drank several times weekly to several times monthly in 1st trimester, while the numbers were slightly above 1% in 2nd and 3rd trimester.

The total raw scores ranged from 8.9-56.0 (Mean =21.0, SD=7.4) for the Fussy baby scale (ICQ), and from 30.0-82.0 (Mean 39.0, S.D=6.2) for the ASQ. Outliers were not omitted from the analyses, as extreme scores might be associated with the exposure. Gestational age distribution was investigated for women exposed gw 9-40; Mean= 15.0, SD= 5.7, range: gw 9-32. SCL-8 at 6 months ranged from 8 to 28 (Mean = 9.8, SD. =2.7), and child’s age when questionnaire was completed ranged from 6.03-10.8 (Mean = 7.0, SD. = 0.8). Only 2.6 % were born preterm; gw 25-36, none of whom were situated in the true infected groups (ILI + positive HI titer). Converting the currently used ASQ scores to the original scaling (0, 5, 10), yielded a total mean score of 248.8 (SD. 31.8) for the current sample, compared to the manual mean of 237.8 (SD. 32.8) for a sample of randomly selected Norwegian children.

(Tables 1-2)

* 1. *Fussy baby scale (ICQ)*

There was no clear overall relationship between exposure to influenza according to gestational length and child temperament (model 1, Table 3, overall p = 0.10). Still, at subgroup level, children who were exposed to maternal influenza during gw 0-8, and also in the weeks just prior to gestation, obtained higher scores on the temperamental scale, indicating more difficult temper. The same was true to a lesser degree for children whose mothers were seronegative but reported an ILI during gw 9-40.

(Table 3)

Although children exposed to maternal H1N1 infection at any time during gestation scored higher on difficult temperament than did non-exposed children (data not shown in Table (B=0.26, CI= -0.05, 0,82, p=0.06)), the ‘test of model effects’ of exposure in this supplementary model indicated no clear overall association between influenza and difficult temper (overall p = 0.25). Likewise, supplementary analyses categorizing the pregnancy into trimesters neither showed a clear overall association, although children exposed in 1st trimester tended to have increased temperamental scores (B=0.29, p= 0.06, data not shown in table).

* 1. *Psychomotor development (ASQ)*

Dividing maternal exposure to influenza into early (gw 0-8) and later (gw 9-40) periods of gestation yielded an overall association of p = 0.03 for the predictor variable as a whole, between exposure and psychomotor development scores in the child (Table 7). At subgroup level, children of seropositive mothers reporting early ILI (gw <0 and gw 0-8) scored about one quarter of a SD poorer on the psychomotor scale than children of unexposed mothers, which indicates a small effect. Conversely, reported ILI during gw 9-40 (irrespective of serologic status) was associated with somewhat improved scores on the ASQ scale, indicating favorable developmental scores. Supplementary analyses run in a reduced sample with additional covariates (i.e. birth complications, nutritional variables) did not change the results. Also, sensitivity analyses with and without gestational length as covariate yielded results that were virtually identical.

To avoid extensive multiple testing, our results rely on the total ASQ score rather than on scores from each of the five ASQ subdomains. However, supplementary analyses of the subdomains revealed that the clearest negative tendency related to early exposure was found in the fine motor subdomain (B = 0.34, p = 0.03), while the largest negative effect related to late exposure was found for the communication subdomain- approaching a medium effect size (B = 0.47, p = 0.02) (data not shown in Table).

(Table 4)

There was no overall difference between exposure groups in the supplementary model (exposure any time in pregnancy, p = 0.57)), and no noticeable differences at subgroup level. The same was found for pregnancy trimesters (all data not shown in Table).

1. **Discussion**

In this population-based study we followed a cohort of women that were pregnant during the 2009 pandemic influenza outbreak. The pandemic offered a unique window of opportunity to study the impact of pandemic influenza in pregnancy. We studied temperament and psychomotor development among 6 months old children exposed to pandemic influenza H1N1 infection in utero, compared to non-exposed children. Children whose mothers had influenza symptoms during the first weeks of pregnancy and positive H1N1-serology at delivery, had poorer psychomotor development scores compared with other children.  These children also had higher scores on the fussiness temperament scale. The present findings represent, to the best of our knowledge, the first report linking serologically confirmed maternal influenza infection during pregnancy to child psychomotor development at 6 months.

* 1. *Interpretation and comparison with other studies*

Previous studies on prenatal infection and child development have mostly focused on adverse birth outcomes [17,29,30]. However, there are also some studies on gestational influenza and neurodevelopment, including reports of lower IQ scores and increased rates of autism, psychoses and affective disorders in adulthood [2,5,7,31]. Impaired cognitive functioning is central to such conditions, thus gestational influenza seems to play a role in the development of cognitive deficits [32]. Studies on serologically confirmed prenatal influenza exposure have reported lower verbal IQ, executive dysfunction and other deficits in cognitive functioning for exposed schizophrenic patients, compared to unexposed cases, also prior to the onset of schizophrenia [33,34].

Cognitive development is difficult to assess at 6 months, as the repertoire of measurable cognitive functions is limited. The ASQ scale measures psychomotor abilities, and may thus be a proxy for neuropsychological development. Hence, it is an outcome closer to cognition than is temperament. The fact that children of mothers reporting ILI in early pregnancy had scores indicating a clearer association for ASQ than temperament is consistent with the assumption that cognitive functioning is more vulnerable to this exposure than emotional functioning. Furthermore, the fact that the strongest association was found in the fine motor domain is logical, given that motor skills belong to the most developmentally sensitive domain the first year of life. Still, it is important to point out that in clinical terms a difference of 0.3-0.4 fractions of a S.D on the ASQ scale is not evident of developmental delay; these children all score well within the normal range of this outcome and the findings do not have clinical implications.

Previous research highlights the importance of timing of influenza exposure for cognitive development in the offspring. As briefly mentioned, earlier studies pointed to mid pregnancy as a critical stage for infection-mediated disturbances [10]. However, shortcomings of design and methodology undermined the validity of such reports [11,35], and later prospective approaches with sera collected throughout pregnancy have suggested that the window with maximal vulnerability to infection-mediated disturbances is earlier than 2nd trimester [11.] Studies on schizophrenia imply a 7-fold increased risk with exposure during 1st trimester, and no increased risk at a later stage [36]. Also, studies on reproductive infections imply an increased risk only if the exposure happens around conception or in the first gestational weeks [37]. The current results support the notion of increased vulnerability during the early stage of the 1st trimester. When expanding the window of influenza exposure from gw 0-8 to 0-12, the association disappeared, as children exposed late in 1st trimester did not have poorer psychomotor scores.

Interestingly, a study on IQ-scores of male conscripts who were in utero during the 1969-1970 Hong Kong flu pandemic in Norway showed that males who were at risk of exposure during first trimester scored slightly lower than males born during the same calendar months in adjacent years [7]. There was a tendency towards lower scores proportionally with earlier timing of exposure. Along the same lines, exposure to infection during early stages of gestation has been related to an increased risk of autism and adult psychotic illness [2,9,38].

The mechanisms by which gestational infection might affect fetal brain development are unknown, though a number of studies indicate that hyperthermia may be harmful to the fetus [39]. Further, in animal studies, viral infection mimics may induce maternal immune activation (MIA), resulting in abnormal brain structure and behavior in animal offspring [1,13,14,40]. Accordingly, the pathway could lead through harmful maternal and fetal inflammatory responses [41].

The current findings may stem from maternal immune activation during a vulnerable period of fetal development [42,43]. An early immune activation may affect fundamental neurodevelopmental processes like cell proliferation and differentiation, and negatively affect cell migration and synapse maturation in developing neurons, compared to a later immune activation [11,44,45].

Interestingly, although a lack of statistical power prevented any firm evidence of an association for exposure shortly before conception, the results suggest that pre-conceptional influenza may also be associated with poorer psychomotor scores at 6 months. This is in support of previous findings suggesting adverse impact on fetal neurodevelopment resulting from pre-conceptional infection [34]. The biological processes related to the maternal immune response after an infection may last a while, and increased levels of proinflammatory cytokines in the mother’s body at the time of conception may therefore explain the mentioned findings, although the insult happened pre conception.

Late exposure showed trends of improved scores. Experimental studies have shown that different prenatal exposures –like influenza and cortisol – may produce similar alterations at both anatomical and molecular levels [32]. Interestingly, in accordance with our findings, Davis & Sandman [46] reported poorer child cognitive performance related to early prenatal cortisol exposure and accelerated performance related to late exposure. The link between infection and stressors may be inflammatory cytokines, as both animal and human studies found circulating and central expression of those to increase after acute psychological stressors [47,48].

No adverse results were found for children of seropositive mothers without reported ILI, on either outcome. This could imply that these women were infected prior to pregnancy rather than during (see limitations), and that their children therefore were non-exposed. Alternatively, subclinical maternal illness is likely underreported, and other factors related to more severe symptoms (e.g. hyperthermia) may be involved in the reported negative effects [39].

* 1. *Strengths and limitations*

The participating women were somewhat more highly educated than the overall pregnant population. Although pandemic infection strikes quite arbitrarily, the consequences of an infection could vary within different population groups (stress and the ability to recover, compensating stimuli of the child etc.). The study’s participation rate at 6 months could potentially cause selection bias, however Monte Carlo simulations have shown that association estimates generally are quite robust against selective non-response [49]. Likewise, a study on self-selection into the Norwegian Mother and Child Cohort study (comparable to NorFlu) concluded that the prevalence of estimates of variables are biased due to self-selection, but not the estimates of associations between variables[50]. The relatively low number of women exposed in the third trimester due to timing of the study inclusion period relative to the pandemic period in Norway may have reduced the chances to detect effects related to late exposure, thus the findings may be generalizable mainly to women exposed early in pregnancy. Although infected women may have been more likely to participate, we do not expect potential selective participation to influence the associations as we compare exposed to non-exposed women, confirmed by serology. Further, as the women knew they had been infected, reporting bias could potentially influence maternal scoring. However, there is no reason why women who knew they were infected later in pregnancy would not report similarly to those infected earlier. The model contained many covariates, and in order to reduce the number of variables in the model, analyses were also run with all somatic conditions collapsed into a “chronic condition” variable as confounder. This did not change the estimates.

The precision of classification of infection is usually less reliable in epidemiological than in clinical studies. In this study, we were able to more reliably categorize infected women due to information from the various sources, including HI titers, questionnaires and independently collected registry data. Still, the classification is partly based on self-reported ILI, and although validated against HI antibody, sero-positivity might in some cases have reflected exposure prior to, rather than during, pregnancy. However, the H1N1 virus only became widespread in the autumn of 2009 and only a low proportion of the seropositives are expected to have been previously infected [51]. Moreover, in this period, the proportion that tested positive for H1N1 was high among persons with ILI in the Norwegian surveillance, indicating that other pathogens were not causing much ILI at the time. On the other hand, the antibody response may have waned to undetectable levels by the time of sampling. Some cases of infection, without ILI, may thus have been misattributed as non-infected. Further, given the massive focus on influenza and potential health risks of pregnant women during the pandemic, we believe that the focus of pregnant women to influenza-like symptoms were heightened, and their recollection more valid, in terms of reporting timing of illness than in a regular influenza season. Further, given that the pregnancy start date was estimated based on various methods, including ultra sound due date and LMP (last menstrual period), limitations associated with the use of LMP should be noted. There may be be some misclassification of gestational age (GA) leading to some possible exposure misclassification for cases where we calculated GA by LMP, but this applies only for a very small number of women missing ultra sound due date from MBR.

The validated outcome scales are both suitable for measuring motor skills, emotion regulation and child responses. As the outcomes rely on parent-completed scales, some random misclassification might occur. Further studies should aim at conducting expert administered neuropsychological assessments in older children with more developed cognitive repertoire. In the current study we have compared scores on cognitive outcome scales for children whose mothers were or were not exposed to pandemic influenza during pregnancy. Interpreting the effect size of continuous outcome scales might not be as straightforward as interpreting risk estimates for dichotomous outcomes. The effect sizes in the current study generally hovered around 0.2-0.3 fractions of a SD, which resembles a small effect [cf. 52]. With an effect size of about 0.2, 58 % in the exposure group will have scores higher than the mean score of the comparison group.

We have not corrected for multiple comparisonsthus the risk of obtaining false positive effects are present and the p-values may potentially be misleading. However, in a hypothesis generating study like this, we consider the possible risk of obtaining false positive effects as more acceptable than risking false negative effects by utilizing methods that quite probably might overcorrect the results. From a medical point of view, we believe the latter would be more unfortunate as we thereby could risk ignoring potential detrimental effects in an exploratory study investigating vulnerable gestational stages.

Overall, the results should be interpreted with great caution because of moderate results. We believe our categorization of the exposure into very early, early and later infection is logical, but *a priori* this is not the only sensible grouping. Therefore, we also presented results from analyses not discriminating on timing of exposure, and these results were generally inconclusive. Consequently. our results should be regarded as hypothesis generative.

**Final disclosure**

No conflict of interests declared.

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