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Examining the association between maternal analgesic use during pregnancy and risk of psychotic symptoms during adolescence

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ABSTRACT

Background: Children and adolescents who report psychotic symptoms in non-clinical samples are at an increased risk of developing schizophrenia. Study of such 'high risk' groups may increase our understanding of early risk factors for psychotic illnesses. Maternal infection during pregnancy is associated with an increased risk of schizophrenia in the offspring, and it has been hypothesised that exposure to maternal intake of analgesics during pregnancy, taken to alleviate the symptoms of viral infections, may partly explain this association. The aim of this study was to examine the relationship between maternal use of aspirin and other analgesics during pregnancy and the occurrence of psychotic symptoms in the offspring.

Methods: This was a longitudinal study of 6437 children belonging to the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort who participated in the psychosis-like-symptoms semi-structured interview (PLIKSi) at 12 years of age. Data on in-utero exposure to analgesics were obtained from self-report questionnaires completed by the mothers during pregnancy.

Results: Increasing frequency of aspirin use during pregnancy was associated with an increased risk of psychotic experiences (adjusted OR 1.44, 95% CI 1.08–1.92). Risk was highest in those whose mothers used aspirin most days or daily (adjusted OR 2.79, 95% CI 1.27–6.07). Paracetamol and other analgesic use during pregnancy were not associated with the risk of offspring psychotic symptoms.

Conclusions: Medications such as aspirin that interfere with the prostaglandin pathway, taken during pregnancy, may influence the risk of schizophrenia in the offspring. Other epidemiological studies are needed to examine this association further.

1. Background

Children and adolescents reporting psychotic symptoms appear to be at increased risk for psychotic disorders in adulthood (Poulton et al., 2000). They may represent a 'high risk' group for psychotic illness and used to explore early risk factors for psychosis vulnerability (Kelleher, et al., 2008; van Os, et al., 2009).

An association between prenatal exposure to influenza or other infections and schizophrenia in later life has been observed in several epidemiological studies (Barr et al., 1990; Boksa, 2008; Brown et al., 2000; Byrne et al., 2007; Edwards, 2007; Fatemi and Folsom, 2009; Fruntes and Limosin, 2008; Sorensen et al., 2009). There is some evidence that this effect

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is greatest for exposure during the second trimester of pregnancy (Limosin et al., 2003), similar to that for exposure to famine in-utero, indicating that this might be a particularly sensitive period of risk to the developing foetal brain (Brown and Susser, 2008). However, serious viral infections during childhood have also been associated with the risk of schizophrenia (Dalman et al., 2008). An association between viral infections during pregnancy and risk of developing psychotic experiences in a non-clinical sample of adolescents has also been reported (Zammit et al., 2009a), although trimester-specific effects were not observed.

There are a number of possible mechanisms that might explain the association between exposure to infection in-utero and risk of psychosis, including direct toxic effects of infectious agents on foetal brain development, harmful effects of hyperthermia or cytokine production, or from adverse effects of medication. A study based on the Copenhagen Perinatal Cohort showed that prenatal exposure to analgesics in the second trimester was associated with a four-fold increased risk of schizophrenia after controlling for maternal viral infection during pregnancy (Sorensen, et al. 2004). The authors hypothesised that maternal intake of analgesics during pregnancy taken to alleviate the symptoms of viral infections may influence schizophrenia risk in the offspring.

It has been postulated that abnormalities in prostaglandin signalling and altered neuronal membrane phospholipids may increase the risk of schizophrenia (Skosnik and Yao, 2003). Viral infections interfere with the prostaglandin mediated immune pathway (Hillbrand et al., 1997). However, it is also possible that maternal intake of medication that effects the prostaglandin pathway, such as aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs), may influence the risk of schizophrenia in the offspring. Exposure in-utero is likely to be a period where the immature brain is particularly sensitive to a range of environmental influences, and it is plausible that this reflects a critical period during which exposure to analgesics might disrupt foetal neurodevelopment.

The aim of this study was to examine the relationship between maternal use of aspirin and other analgesics during pregnancy and the occurrence of psychotic symptoms in the offspring. We also aimed to examine whether any effects observed were independent of potential confounding, and whether they were trimester-specific.

2. Method

2.1. Sample

This study examines data from the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort. The cohort was set up to examine genetic and environmental determinants of health and development (Golding et al., 2001). The initial cohort consisted of 14,062 children born to residents of the Bristol area, UK, who had an expected date of delivery between 1st April 1991 and 31st December 1992 (www.alspac.bris.ac.uk) The parents completed regular postal questionnaires concerning their child's health and development since birth. The children have attended annual assessment clinics since age 7 years.

This study examines data from 6437 children who participated in the psychosis-like-symptoms (PLIKS) semi-structured interview (PLIKSi) (Horwood et al., 2008) when they were 12 years of age. Due to attrition and non-response, sample sizes vary according to the exposures and datasets examined, with 4571 individuals included in the final fully-adjusted model.

2.2. Measures

2.2.1. Outcomes

PLIKSi examines past 6-month occurrence of hallucinations (visual and auditory), delusions (delusion of being spied on, persecution, thoughts being read, reference, control, grandiose ability and other unspecified delusions), and experiences of thought interference (thought broadcasting, insertion and withdrawal). For these 12 core items, 7 screening (stem) questions were derived from DISC-1 V (Shaffer et al., 2000) and 5 questions from SCAN version 2.0 (WHO, 1994) modified slightly after piloting (further detail available at http://www.bris.ac.uk/psychiatry/staff/zammit/).

Coding of all items followed the glossary definitions and rating rules for SCAN, and clinical cross-questioning and probing by psychologists trained in using the PLIKSi was used to establish the presence or absence of symptoms. Interviewers rated symptoms as either not present, suspected or definitely present. Unclear responses after probing were always 'rated down', and symptoms only rated as definite when a convincing example was provided. In the analysis symptoms were included if they were not attributable to sleep, fever or substance intoxication, consistent with the approach of classification systems for diagnosis of functional psychotic disorders. The average kappa value for inter-rater reliability was 0.72. For the purpose of this study our primary outcome was the presence of any suspected or definite psychotic symptom compared to none (i.e. a binary variable). As secondary analyses we also examined a binary outcome of presence of any definite psychotic symptom compared to suspected or none.

2.2.2. Exposures

Data on maternal use of analgesics during pregnancy were obtained from self-report postal questionnaires completed by the mother at median gestation of 18 weeks (90% 18 to 26 weeks) and 32 weeks (90% 32 to 36 weeks). Women were asked about whether they had used any medications for 15 common problems (for example nausea, sleeping problems, infection, anxiety, depression, and pain), as well as about use of any medication for any other reasons. There were also questions regarding the frequency of use of the following specific medications: i) aspirin, ii) paracetamol, iii) codeine or anadin, iv) mogadon or other sleeping tablets, and v) valium or other tranquilisers. Maternal analgesic use was coded according to the type of analgesic used (aspirin use, paracetamol use, and other analgesic use) and frequency of use (none/sometimes/most days or daily use). Questions from the 18 week questionnaire enquired about use since pregnancy began, whereas those from the 32 week questionnaire enquired about use over the previous 3 months. This data therefore allowed us to examine whether effects for each analgesic were different between the first half and second