

Association between prenatal exposure to analgesics and risk of schizophrenia

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Background Disturbances in the central nervous system originating during foetal life may increase the risk of schizophrenia.

Aims To illuminate the hypothesis that prenatal exposure to analgesics may affect foetal neurodevelopment, leading to increased risk of schizophrenia in adulthood.

Method Using data from the Copenhagen Perinatal Cohort and from the Danish Psychiatric Central Register, we studied the relationship between prenatal exposure to analgesics and the risk of schizophrenia. The effect of prenatal exposure was adjusted for parental history of schizophrenia, second-trimester viral infections, concomitant drug treatment during pregnancy, an index of pregnancy complications, parental social status and parental age.

Results In a risk set of 7999 individuals, 116 cases of schizophrenia were found (1.5%). Prenatal exposure to analgesics in the second trimester was associated with an elevated risk (adjusted odds ratio 4.75, 95% CI 1.9–12.0). Independent of the covariates, the effect remained statistically significant.

Conclusions Independent of a wide range of possible confounders, a significant association between second-trimester exposure to analgesics and increased risk of schizophrenia was observed.

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Studies strongly suggest that genetic transmission accounts for most of the familial aggregation of schizophrenia (Gottesman, 1991; Kendler & Diehl, 1993). Environmental risk factors have also been implicated: these include pregnancy and delivery complications (Parnas *et al*, 1982; Geddes & Lawrie, 1995) and influenza during the mother's pregnancy (Mednick *et al*, 1988; O'Callaghan *et al*, 1991; Kunugi *et al*, 1992; McGrath *et al*, 1994). Some studies have been unable to confirm an association between prenatal exposure to influenza and later schizophrenia (Crow *et al*, 1991; Selten & Slaets, 1994; Susser *et al*, 1994), and it is conceivable that maternal intake of medication during pregnancy to alleviate symptoms associated with influenza and similar diseases might influence the risk of schizophrenia in the offspring. Thus, maternal intake of analgesics might be related to the offspring's risk of schizophrenia. To our knowledge, no study linking psychiatric morbidity in the offspring with maternal intake of analgesics during pregnancy has been reported; we therefore analysed data from the Copenhagen Perinatal Cohort to examine the associations between schizophrenia in adult life and prenatal exposure to analgesics.

METHOD

The Copenhagen Perinatal Cohort

The Copenhagen Perinatal Cohort consists of 9125 individuals delivered by 8949 pregnant women between October 1959 and December 1961 at the maternity department of the Copenhagen University Hospital, Rigshospitalet. A total of 8400 infants survived the first month after birth. Information on exposure to analgesics and psychiatric hospitalisation was available for 7999 individuals (4098 males and 3941 females) from the Perinatal Cohort.

Consumption of medication during pregnancy

The mothers' reported use of medication during pregnancy (information obtained in prenatal and postnatal interviews on any medication taken for at least 5 days) was computerised, using binary indicator variables without dosage information. The following types of drugs were included in this self-report: antihistamines, barbiturates, psychoactive medications (this category included meprobamate, chlorthalidone, glutethimide, chlorpromazine or perphenazine, imipramine and reserpine), analgesics, chemotherapeutics (sulphonamides, nitrofurantoin or phenyl salicylate preparations for disinfection of the urinary tract), hormones (this category included oestrogens, progestogens and corticosteroids) and diuretics.

The category of analgesics was pharmacologically heterogeneous. It included both prescribed analgesics and analgesics bought over the counter, and it was not possible to separate analgesics used for treating fever from those used for treating pain. Aspirin and other antipyretics were commonly used; other analgesics included phenacetin, aspirin in combination with codeine and, more rarely, stronger analgesics such as morphine or synthetic forms of morphine. The category of analgesics also included mixed-formula drugs containing aspirin-like analgesics in combination with a smaller amount of opioid analgesic. Other combinations included two types of anti-inflammatory drugs (for instance antipyrine plus phenacetin) and analgesics in combination with caffeine.

The mothers were asked about their intake of analgesics in the first, second and third months and in the second and third trimesters of pregnancy. For the study population of 7999 cohort members, the missing data rate was less than 1% for the first and the third months of pregnancy, and 4.4% for the second month. Information on use of analgesics was complete for the second trimester, while the missing data rate was 1.7% for the third trimester. The prevalence of exposure to analgesics at any time during the first trimester was 0.9% (71/7997), during the second trimester 1.8% (144/7999) and during the third trimester 2.0% (154/7867). Nineteen individuals were exposed exclusively during the first trimester, 58 were exposed exclusively during the second trimester and 82 were exposed exclusively during the third

trimester, while 41 were exposed in all three trimesters.

Demographic factors

Maternal age (in years) at the time of delivery was obtained from the records at Rigshospitalet. Information on social status was obtained from an interview with the mother when the child was 1 year old. The socio-economic classification was based on information about breadwinner's occupation, breadwinner's education, type of income (wage or salary) and quality of housing. Sufficient data for classification of social status were available for 6333 individuals (79.2% of the study population). The overall social status mean was substituted for missing data, and a dummy variable was included to indicate missing data on social status in the logistic regression analyses.

Psychiatric hospitalisation

Written approval to conduct a registry-based psychiatric follow-up was obtained from the regional scientific ethics committee. The Danish Psychiatric Central Register has been computerised since 1 April 1969 (Munk-Jørgensen & Mortensen, 1997). It contains data on all admissions to Danish psychiatric in-patient facilities. The diagnostic system in use when the Danish Psychiatric Central Register was computerised was the ICD-8 (World Health Organization, 1967). The cohort members and their parents were followed in the Danish Psychiatric Central Register to identify all hospital admissions with a diagnosis of schizophrenia (ICD-8 code 295 or ICD-10 code F20) until December 1999. In ICD-8, schizophrenia is defined by prototypic descriptions of symptoms, such as bizarre delusions, delusions of control, abnormal affect, autism, hallucinations and disorganised thinking. In 1994, the more operational ICD-10 criteria were implemented (World Health Organization, 1992). The cohort and their parents were categorised as having a history of schizophrenia (ICD-8 code 295 or ICD-10 code F20) if they had been admitted with one of these diagnoses.

Other variables

Weighted pregnancy and delivery complications scales were constructed for use with the Copenhagen Perinatal Cohort by a team of American and Danish obstetricians and

paediatric neurologists (Zachau-Christiansen & Ross, 1975). To control for pregnancy complications, we used the pregnancy complications scale, which included items such as bleeding or illness during pregnancy, use of radiation during pregnancy and pre-eclampsia. Data on viral infections in the second trimester were available for 7970 pregnancies (99.6% of the study population). A few days after delivery, the mothers were asked about infections during the different periods of pregnancy, and the vast majority of viral infections recorded were minor respiratory illnesses or influenza (Villumsen, 1970).

We have recently reported that the combination of maternal hypertension and third-trimester (but not second-trimester) intake of diuretics during pregnancy was associated with an elevated risk in the offspring of schizophrenia according to the ICD-8 classification (Sørensen *et al*, 2003). Both second-trimester and third-trimester exposures to diuretics were included as potential confounders.

Statistical analysis

For each recorded period of gestation (first, second and third months and second and third trimesters), we estimated the risk of developing schizophrenia in cohort members exposed to analgesics (exposure group) and in those who were not exposed to these drugs (non-exposure group). Sub-periods showing an odds ratio significant at the 5% level were included in the subsequent multivariate analyses.

The distributions of potential confounders, including parental demographic and psychiatric characteristics, were compared between the two groups. One-way analysis of variance was used to compare the distributions of the continuous variables: parental age, parental social status and Pregnancy Complications score. Chi-squared tests were used to compare the proportions of exposures to viral infections (second trimester), classes of medication in the second trimester, and the proportions of maternal and paternal schizophrenia in the exposure and non-exposure groups.

The risk of developing schizophrenia associated with prenatal exposure to analgesics was estimated in multivariate logistic regression models. The multivariate analyses included exposure to analgesics in the first and second trimesters and the following binary variables: second-trimester exposure to viral infections, other

medication in the second trimester (anti-histamines, psychoactive medications, barbiturates, chemotherapeutics, hormones and diuretics) and third-trimester exposure to diuretics. In addition, maternal and paternal schizophrenia were included as covariates, and the following parameters were included as continuous covariates: maternal and paternal age, parental social class and Pregnancy Complications score. The first model adjusted for parental age, social status and Pregnancy Complications score, whereas the second model (full model) studied the joint effects of all the variables listed.

RESULTS

A total of 116 cases of schizophrenia (cumulative incidence 1.5%) were identified. Among 4058 male cohort members, 76 (1.9%) had developed schizophrenia, and among 3941 female cohort members, 40 (1.0%) had developed schizophrenia.

Table 1 shows that exposure to analgesics in the registered sub-periods of gestation was associated with an elevated risk of schizophrenia. For the first trimester the odds ratio was only significant for the third month. The odds ratio was also not significant for the third trimester, whereas the cumulative incidence of schizophrenia in the exposure group in the second trimester was significantly higher than in the non-exposure group in that period (5.6% *v.* 1.4%; *P* < 0.001). Thus, the odds ratio for the second trimester was 4.22 (95% CI 2.0-8.8).

Some cohort members were exposed to analgesics in more than one period of gestation. The total number of cohort members who had been exposed at any time during gestation was 245 (ever exposed), whereas 7754 had never been exposed. The unadjusted odds ratio associated with exposure to analgesics at any time during gestation was 2.39 (95% CI 1.2-5.0), whereas it was 2.71 (95% CI 1.3-5.4) when adjusted for social status, mother's and father's age, and Pregnancy Complications score. Table 2 shows the distribution of demographic and other characteristics of individuals who had ever been exposed to analgesics during gestation *v.* the non-exposed comparison group. Exposure correlated with viral infections, antihistamine intake, barbiturate intake and use of psychoactive medication. Moreover, the mean parental age and the mean Pregnancy

Table 1 Risks of developing schizophrenia in members of the Copenhagen Perinatal Cohort associated with exposure to analgesics during gestation

Period of pregnancy	Exposed to analgesics		Not exposed to analgesics		
	Cohort members <i>n</i>	Cumulative incidence of schizophrenia <i>n/N</i> (%)	Cohort members <i>n</i>	Cumulative incidence of schizophrenia <i>n/N</i> (%)	Odds ratio (95% CI)
First month	45	2/45 (4.4)	7951	114/7949 (1.4) ¹	3.20 (0.8–13.4)
Second month	55	2/55 (3.6)	7644	111/7641 (1.5) ¹	2.56 (0.6–10.6)
Third month	63	3/63 (4.8)	7933	113/7931 (1.4) ¹	3.46 (1.1–11.2)*
Second trimester	144	8/144 (5.6)	7855	108/7855 (1.4)	4.22 (2.0–8.8)**
Third trimester	156	5/156 (3.2)	7711	111/7711 (1.4)	2.27 (0.9–5.6)

1. A few members of the cohort could not be checked in the Psychiatric Register.

* $P < 0.05$, ** $P < 0.01$.

Table 2 Characteristics of the exposure and non-exposure groups of the Copenhagen Perinatal Cohort

	Ever exposed to analgesics during gestation (<i>n</i> =245)	Not exposed to analgesics during gestation (<i>n</i> =7754)	Test statistic (d.f.=1)
Other exposure variables, <i>n/N</i> (%)			
Exposed to antihistamines in second trimester	25/245 (10.2)	478/7754 (6.2)	$\chi^2=6.57^*$
Exposed to barbiturates in second trimester	14/245 (5.7)	246/7754 (3.2)	$\chi^2=4.87^*$
Exposed to psychoactive medication in second trimester	25/245 (10.2)	282/7754 (3.6)	$\chi^2=27.75^{**}$
Exposed to chemotherapeutic drugs in second trimester	12/245 (4.9)	287/7754 (3.7)	$\chi^2=0.95$
Exposed to hormones in second trimester	13/245 (5.3)	250/7754 (3.2)	$\chi^2=3.23$
Exposed to diuretics in second trimester	2/245 (0.8)	64/7754 (0.8)	$\chi^2=0.00$ 1
Exposed to diuretics in third trimester ¹	8/242 (3.3)	399/7621 (5.2)	$\chi^2=1.78$
Exposed to viral infection in second trimester ²	20/242 (8.2)	444/7728 (5.8)	$\chi^2=2.72$
Mother registered with schizophrenia, <i>n/N</i> (%)	4/245 (1.6)	93/7754 (1.2)	$\chi^2=0.37$
Father registered with schizophrenia, <i>n/N</i> (%)	1/245 (0.4)	40/7754 (0.5)	$\chi^2=0.054$
Parental age, years			
Maternal age, mean (s.d.)	27.4 (6.1)	25.8 (6.5)	$F=14.13^{**}$
Paternal age, mean (s.d.)	31.2 (8.2)	29.6 (7.4)	$F=11.17^*$
PC score, mean (s.d.)	6539 (3078)	5760 (2159)	$F=30.26^{**}$
Parental social status, mean (s.d.)	4.0 (1.7)	4.0 (1.6)	$F=0.91$

PC, Pregnancy Complications scale.

1. Total *n*=7863, owing to missing data.

2. Total *n*=7970, owing to missing data.

* $P < 0.05$, ** $P < 0.01$.

Complications score were higher. The two groups did not differ with respect to parental social status or proportions of mothers and fathers with schizophrenia.

The relative risks (odds ratios) associated with exposure to analgesics are shown in Table 3. This table also shows the relative risk associated with exposure

to viral infection or other medication in the second trimester and the risk associated with maternal or paternal hospitalisation with schizophrenia (Table 3, first column). Maternal schizophrenia emerged as the strongest risk factor (adjusted OR=9.27, 95% CI 4.7–18.2). The second strongest effect was noted for second-trimester exposure to analgesics (adjusted OR=4.75, 95% CI 1.9–12.0). The risk of schizophrenia associated with paternal schizophrenia was lower than expected (adjusted OR=3.22, 95% CI 0.7–14.1). Similarly, the risk of schizophrenia associated with second-trimester viral infection was lower than expected (adjusted OR=0.94, 95% CI 0.4–2.2).

Assuming a causal connection between prenatal exposure to analgesics and increased risk of schizophrenia, the attributable risk – i.e. the proportion of individuals in the total population with the disease attributed to exposure to analgesics in the second trimester – was calculated (Altman *et al*, 2000) and found to be 5.2% (95% CI 1.8–11.4).

The effect of analgesics exposure in the second trimester was statistically significant in both genders. The unadjusted odds ratio was 3.77 (95% CI 1.5–9.6) in males and 4.94 (95% CI 1.6–16.4) in females.

Second-trimester analgesics exposure and other putative risk factors

Out of 7970 cohort members, 464 (5.8%) had been exposed to a viral infection during the second trimester. Six cases of schizophrenia (1.3%) emerged among those exposed. There was no interaction between second-trimester exposure to analgesics and second-trimester viral exposure in relation to outcome. Only 15 cohort members had both these exposures during the second

Table 3 Multiple logistic regression analysis of exposures during pregnancy and of parental psychiatric diagnoses predicting schizophrenia

Prenatal variable	Unadjusted odds ratio (95% CI)	Model 1 odds ratio (95% CI) ¹	Model 2 odds ratio (95% CI) ²
Medication			
Analgesics			
First trimester	3.05 (1.0–9.8)	3.06 (0.9–9.9)	0.98 (0.2–4.1)
Second trimester	4.22 (2.0–8.8)	4.32 (2.1–9.1)	4.75 (1.9–12.0)
Antihistamines			
Second trimester	0.88 (0.4–2.0)	1.00 (0.5–2.2)	0.95 (0.4–2.2)
Barbiturates			
Second trimester	0.79 (0.3–2.4)	0.80 (0.3–2.6)	0.77 (0.2–2.5)
Psychoactive medication			
Second trimester	1.37 (0.6–3.2)	1.42 (0.6–3.3)	1.10 (0.5–2.7)
Chemotherapeutic drugs			
Second trimester	0.46 (0.1–1.8)	0.44 (0.1–1.8)	0.44 (0.1–1.8)
Hormones			
Second trimester	1.05 (0.4–2.9)	1.16 (0.4–3.2)	1.24 (0.5–3.5)
Diuretics			
Second trimester	1.05 (0.2–7.6)	1.10 (0.2–8.1)	0.64 (0.1–5.1)
Third trimester	1.76 (0.9–3.4)	1.87 (1.0–3.6)	2.09 (1.1–4.2)
Other variables			
Viral infection			
Second trimester	0.88 (0.4–2.0)	0.91 (0.4–2.1)	0.94 (0.4–2.2)
Parental schizophrenia³			
Mother affected	9.50 (4.9–18.3)	9.14 (4.7–17.7)	9.27 (4.7–18.2)
Father affected	3.53 (0.8–14.8)	3.29 (0.8–13.9)	3.22 (0.7–14.1)

1. Model 1 adjusted for mother's and father's age, parental social status and Pregnancy Complications scale score.
 2. Model 2 adjusted for mother's and father's age, parental social status, Pregnancy Complications scale score and for all of the variables listed. Model outputs were calculated on the basis of $n=7835$, owing to missing data for the variables analgesics (first trimester), diuretics (third trimester) and viral infection (second trimester).
 3. Parent admitted to hospital with schizophrenia.

trimester of gestation, none of whom had a subsequent diagnosis of schizophrenia.

Second-trimester exposure to medication other than analgesics did not confer an elevated risk of schizophrenia, but third-trimester exposure to diuretics was significantly associated with risk of the disease in the multivariate analysis (adjusted OR=2.09, 95% CI 1.1–4.2). The association between exposure to psychoactive medication in the second trimester and outcome was in the expected direction but was not statistically significant. Mothers who took many analgesics might be at higher risk of developing an affective disorder or a substance dependence disorder later in life. Assuming that many with such diagnoses would have been in contact with a psychiatric in-patient facility in Denmark after 1969, we decided to carry out additional analyses in a subsample of 6109 cohort members whose mother and father did not appear in the Danish

Psychiatric Central Register. Those excluded were all offspring of mothers or fathers with a diagnosis of schizophrenia or any other psychiatric disorder. In the subsample the unadjusted odds ratio of developing schizophrenia associated with prenatal exposure to analgesics in the second trimester was 4.51 (95% CI 1.6–12.7).

Out of 144 members of the subsample who had been exposed to analgesics at any time during gestation, 18 people had been exposed to opium or morphine, and 2 cases of schizophrenia (11.1%) arose in the latter subgroup. A preliminary review (data not shown) of some of the original data forms indicated that some of the opioid-treated mothers had undergone abdominal surgery a short time before. The Pregnancy Complications score for these women was higher than the scores for the cohort as a whole (data not shown). We found no indication in the data forms that any of these women had ever misused opioids.

A subgroup of the cohort ($n=45$) had been exposed to mixed-formula analgesic drugs that contained, among other things, older pyrazolone derivatives (antipyrine, isopropylantipyrine, salipyrine, phenazone, propyphenazone). Four cases of schizophrenia (8.9%) arose in that subgroup. The unadjusted odds of developing schizophrenia was 6.74 (95% CI 2.4–19.1) in those who had been exposed to mixed-formula analgesics of this sort and the estimate remained significant when we adjusted for maternal and paternal age, social status and Pregnancy Complications score.

DISCUSSION

Independent of a wide range of potential confounders, an association between prenatal exposure to analgesics and risk of schizophrenia was observed. The estimate of the risk of schizophrenia was more than four times greater in individuals who were exposed to analgesics in the second trimester (the association was slightly stronger in females than in males). The association was independent of maternal schizophrenia, which was the strongest risk factor for schizophrenia in this study.

From a methodological viewpoint, our prospective study is well suited to examine putative associations between prenatal exposure to medication and adverse outcomes many years later. Exposure to drug treatment was recorded shortly after delivery, thus minimising the risk of recall bias. The fact that only hospitalised cases of schizophrenia were identified should not be important, as most individuals meeting ICD-8 or ICD-10 criteria for schizophrenia are admitted to hospital before the age of 40 years. Up to 1994, the (ICD-8) concept of schizophrenia in Denmark reflected diagnostic caution rather than over-inclusiveness. By extending the period of follow-up beyond 1994, some new cases of schizophrenia were identified using the more operational ICD-10 criteria.

We are not aware of any previous study suggesting a link between prenatal exposure to analgesic drugs and increased risk of severe mental illness. Tentatively, three types of explanations may be considered:

- (a) chemical substances might have caused a subtle disruption of foetal neurodevelopment (or interacted with yet unknown genetic liability factors for

the disorder) to increase the risk for later development of schizophrenia;

- (b) maternal somatic conditions for which the mothers took analgesics during pregnancy might underlie the observed association;
- (c) the association could be explained by unidentified factors (which could not be fully controlled in the analysis) that correlate with both maternal intake of analgesics during pregnancy and outcome (residual confounding).

The unusually high risks of schizophrenia (11.1% and 8.9%, respectively) in the small subgroup of offspring of mothers who were treated with morphine or opioid analgesics and the subgroup with prenatal exposure to mixed-formula analgesics could be interpreted as a possible indication of a drug-related effect. Some of the mixed-formula analgesics contained antipyrine and related substances. The derivatives of these substances undergo extensive metabolism in humans. Little toxicological information on their embryotoxic and teratogenic properties exists for these substances (Burdan, 2002). However, to establish a drug-associated risk of a specific adult outcome in a non-experimental setting requires comparability of the exposed and non-exposed groups. The above-mentioned small subgroups may not be comparable with the pool of non-exposed cohort controls on all the characteristics thought relevant to the development of schizophrenia.

It is attractive to speculate that *in utero* exposure to one or several types of analgesics could be implicated in disruption of foetal neurodevelopment. During the second trimester of pregnancy, the cortical subplate reaches its peak of development (Akbarian *et al*, 1995). This may be a period when the immature brain is particularly sensitive to a range of intrauterine environmental influences.

Based on data from the Copenhagen Perinatal Cohort, Villumsen noted that the incidence of malformed offspring of mothers who did not take medication during pregnancy was 3.6%, whereas the incidence of malformed children in offspring of mothers who had taken analgesics was 7.4% (Villumsen, 1970). This is of potential relevance to theories on aetiological factors in schizophrenia as well. A large number of minor physical anomalies (high-steeped palate, large or small distance between tear ducts, adherent earlobes)

CLINICAL IMPLICATIONS

- Children born to mothers who took analgesics for periods that extended into the second trimester of their pregnancy may have an increased risk of developing schizophrenia.
- The association between prenatal exposure to analgesics and increased risk of schizophrenia was independent of other known risk factors for the disorder.
- It would have required a larger cohort study and the collection of additional prenatal and perinatal data to disentangle effects of prenatal exposure to analgesic drugs from the effects of the somatic and psychosomatic conditions prompting their use.

LIMITATIONS

- The study lacked adequate statistical power to test whether differential effects of particular analgesic substances were present.
- The data on prenatal exposure to medication dates back to the early 1960s and some of the drugs used at that time are now obsolete in most countries.
- No information on the dosage of the drugs taken during the pregnancy was available.

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have been linked to schizophrenia-spectrum disorders in a subsample of the Copenhagen Perinatal Cohort (Schiffman *et al*, 2002). It has even been suggested that common genetic or environmental factors might be associated with schizophrenia and congenital malformations (Goodman, 1996; Ismail *et al*, 1998).

We observed no difference in the proportions of maternal and paternal schizophrenia in analgesic-exposed and non-exposed cohort members. The mothers of the two groups did, however, differ in other important aspects. Maternal intake of psychotropic drugs during the second trimester correlated with intake of analgesics in the same period. Intake of these medications might be associated with higher psychiatric

morbidity and/or a tendency to consult a physician more often. When the cohort was established, few Danish women consumed alcohol and the use of illicit drugs was extremely rare. Consequently, data were not collected on maternal alcohol or illicit drug use during pregnancy.

Maternal viral infection in the second trimester was not significantly associated with schizophrenia, but in this study statistical power might not have been sufficient to detect such a relationship. As mentioned previously, only 15 cohort members had been exposed to both viral infection and maternal analgesics, and consequently statistical power is also a concern when interpreting the non-significance of the interaction between these two factors.

In conclusion, prenatal exposure to analgesics in the second trimester of pregnancy conferred a more than four-fold greater risk of schizophrenia. However, only 6.9% of all the cohort members with schizophrenia had been exposed to analgesics in the second trimester. Replication of this research by other investigators is clearly needed before prenatal exposure to analgesics can be added to the list of demonstrated risk factors for schizophrenia.

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