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Original article

Obstetric complications in distinct schizophrenic subgroups

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Summary – In 55 chronic DSM III-R schizophrenics the occurrence of obstetric complications (OCs) was investigated using the familial/sporadic strategy and Leonhard's unsystematic/systematic distinction. The overall frequency and severity of OCs did not differ between patients and controls. A sub-sample of patients, whose genetic risk was supposed to be high in both classification systems (diagnosis of unsystematic and familial schizophrenia), had significantly fewer OCs than controls on the Lewis and Murray scale ($P < 0.05$). With reference to previous reports of increased mortality rates in the offspring of schizophrenics, high genetic risk and additional perinatal stressors may increase perinatal mortality. In contrast, patients whose genetic risk was supposed to be low in both systems (diagnosis of systematic and sporadic schizophrenia) showed a trend to an increased frequency of OCs in the Fuchs scale. In the context of the recently reported highly significantly increased rate of maternal infections during midgestation in these patients, it was supposed that perinatal complications may be of some aetiological importance in schizophrenics with low genetic risk.

obstetric complications / schizophrenia / familial-sporadic concept / Leonhard classification

Introduction

The influence of pregnancy and obstetric complications (OCs) on the development of schizophrenia during adulthood is a matter of on-going controversy (Goodman, 1988; Lewis, 1989). It is widely accepted that schizophrenics have significantly more prenatal and perinatal complications than their normal siblings (Woerner *et al*, 1973; Eagles *et al*, 1990). This difference persists in schizophrenics with a familial form of the disease (De Lisi *et al*, 1988). Furthermore, congenital risk factors seem to be more common in schizophrenia than in other psychiatric disorders (Pearlson *et al*, 1985; Lewis and Murray, 1987). Parnas *et al* (1982) reported that the offspring of schizophrenic mothers who developed schizophrenia in adulthood had a non-significant increased level of OCs than was the case for those who remained well, and those with schizotypal personality disorder had a significantly decreased level of OCs compared to the schizophrenics. As reviewed by McNeil (1991), children of schizophrenic parents, who are considered to be at increased genetic risk, do not suffer from a substantially increased rate of OCs. The author concluded that OCs are not genetically determined in reproductions among schizophrenics. There are inconsistent results regarding the question as to whether schizophrenics suffer more frequently from OCs and from more severe complications during delivery than do normal controls. Turner *et al* (1986) failed to find any differences between schizophrenics and age-matched controls. Jacobson and Kinney (1980) found an elevated OC level in a sample which had a mainly favourable outcome (Kety *et al*, 1968) as did Gillberg *et al* (1986) in a mixed sample of remitting "teenage psychoses". McNeil and Kaij (1978) reported a significantly increased frequency of obstetric and neonatal complications in a sample of 54 narrowly defined "process schizophrenics". Done's study (1991) was based on a different type of OC scale

than that used in previous studies. This study re-analysed data from the British perinatal mortality survey sample taken in 1958 and found no significantly increased level of complications associated with perinatal death in the birth cohort in those children who subsequently developed schizophrenia.

Wilcox and Nasrallah (1987), Schwarzkopf *et al* (1989), and O'Callaghan *et al* (1990) demonstrated an increased rate of obstetric complications in sporadic schizophrenia compared to familial forms. No significant differences between the two groups were reported by Pearlson *et al* (1985), Nimgaonkar *et al* (1988), and Reddy *et al* (1990). The concept of dividing schizophrenia into familial (positive family history of schizophrenia) and sporadic forms (absence of schizophrenia among first and/or second degree relatives) is often used in psychiatric research (Murray and Reveley, 1985). Using modern diagnostic criteria (APA, 1987), this strategy seems to be the most appropriate way of registering the genetic risk of the disease (Kendler, 1987).

Another strategy dealing with the heterogeneity of schizophrenia was outlined by Karl Leonhard (1979). Continuing the work of Kraepelin, Wernicke and Kleist, he classified schizophrenia into two main categories on the basis of clinical symptom-picture, course and long-term outcome. The unsystematic schizophrenias with acute onset and usually polymorphous symptomatology show a clearly periodic course and lead to varying degrees of residual states. In contrast, the systematic forms with mostly insidious onset run a progressive course leading to severe and irreversible defective states in which no marked change in symptoms is observable (Franzek and Beckmann, 1992). In both groups Leonhard subsequently found a different heredity (Leonhard, 1979, 1980). Unsystematic schizophrenics had a high familial loading with homogeneous psychoses (about 20%). However, a positive family history was mostly missing (1–3%) in systematic schizophrenics. Thus, Leonhard classified unsystematic schizophrenia as a mainly genetically determined disease and systematic schizophrenia as a sporadic, more environmentally induced disease.

Recently, we found a significantly increased rate of maternal infectious diseases during gestation in systematic compared to unsystematic schizophrenias (Stöber *et al*, 1992). On the same sample of patients we now test the hypothesis that obstetric complications are associated with the development of sporadic, and in particular of Leonhard's systematic schizophrenias.

Subjects and methods

Diagnosis in DSM III-R and Leonhard's classification

Interviews were carried out with the mothers of 55 non-related chronic schizophrenics (12 women, 43 men) and 20 age-matched physically and mentally healthy controls, to investigate various adverse events which had occurred during the prenatal, intrapartal and postnatal periods. Demographic and clinical characteristics of the patients and age of their mothers at the time of interview with regard to the various diagnostic groups were described in detail in a previous paper in this journal (Stöber *et al*, 1992). The study started on wards with chronically ill male patients. This explains why men clearly outnumber women in the study. Patients had to fulfill the diagnostic criteria of chronic schizophrenia according to DSM III-R as well as Leonhard's group of schizophrenias. Thus, all patients had an unfavourable outcome with severe residual psychopathology.

Patients fulfilling Leonhard's criteria of cycloid psychoses (Leonhard, 1979), were deliberately not included, even when DSM III-R criteria for schizophrenia were fulfilled. After personal examination, diagnoses were established by H Beckmann and E Franzek. Both psychiatrists are experienced in both the DSM III-R and Leonhard classification systems. In a recent study of chronic schizophrenics, they had a coefficient of agreement (Cohen's kappa) of 0.88 within the Leonhard classification (Franzek and Beckmann, 1992).

The total sample consisted of the following groups:

Familial/sporadic distinction according to DSM III-R
A familial form of schizophrenia was presumed when the patient had a first and/or second degree relative who had formerly received treatment in a psychiatric hospital with a diagnosis of schizophrenia. Therefore, 19 patients had a familial form and 36 a sporadic form of DSM III-R schizophrenia.

The Leonhard classification distinguishing between systematic and unsystematic schizophrenia
H Beckmann and E Franzek independently diagnosed all patients according to Leonhard's classification without considering family history. Unsystematic schizophrenia (mainly genetically determined according to Leonhard) was diagnosed in 32 patients. A systematic form of schizophrenia (mainly environmentally determined according to Leonhard) was found in 23 patients.

"High genetic risk" and "low genetic risk" group: (genetic risk supposed to be similar in both classification systems). Even when strong heredity is supposed, clinical manifestation of the illness may be lacking in predisposed individuals simulating sporadic occurrence of the illness in a given pedigree. Otherwise, familial loading with schizophrenic psychoses is not necessarily due to genetic factors. This led us to form the following subsamples:

Table I. Distribution of obstetric complications among the total schizophrenic sample, the diagnostic subgroups and the controls (obstetric complications scale – Lewis 1987).

			DSM III-R		*Leonhard criteria*	
Obstetric Complications	*Controls (n = 20)*	*Total sample (n = 55)*	*Familial (n = 19)*	*Sporadic (n = 36)*	*Unsystematic (n = 32)*	*Systematic (n = 23)*
Negative	7	24	11	13	16	8
Positive	13	31	8	23	16	15

No statistically significant differences were found. Comparisons were made using the χ^2 test.

a) a subsample of patients (n = 13) of supposed high genetic risk in both classification systems: patients with a diagnosis of familial schizophrenia and unsystematic schizophrenia according to the Leonhard classification.

b) a subsample of patients (n = 17) of supposed low genetic risk in both classification systems: patients fulfilling the criteria for sporadic schizophrenia and systematic schizophrenia in the Leonhard classification.

Controls
None of the 20 controls had a history of major physical or psychiatric illness. In addition, they had no first or second-degree relatives with schizophrenia. At the time of the study, all of them had finished their vocational training and were employed.

Maternal recall
A highly structured interview was developed (Stöber, in preparation). Tilley *et al* (1985) and O'Callaghan *et al* (1990) demonstrated that mothers seem to be reliable informants regarding their children's birth histories, even many years after giving birth. Thus, due to the lack of birth records of all probands, we felt sufficient justification to carry out a retrospective study. Questions were asked about the course of the pregnancy, delivery and postnatal development and all notable events were written down in detail. The interviewer (G Stöber) was not aware of the patient's diagnoses in the Leonhard classification or their family history of psychoses. The interviewer was not allowed to obtain information concerning these issues during the session. This rule was only broken after all 55 mothers had been interviewed and the obstetric complications had been rated.

Obstetric and perinatal complications were rated on the "obstetric and birth complication scale" of Lewis and Murray (1987) and the "severity weight allocation scale for specific complications" of Fuchs (Parnas *et al*, 1982). Each interviewee was thoroughly questioned in accordance with the checklists in the two scales. The first scale (Lewis and Murray, 1987) consisted of a 15-item checklist of complications, scored as 0 (absent), 1 (equivocally present), or 2 (definitely present). At least one definite or equivocal complication was required for allocation to the group that experienced obstetric complications. This scale does not permit complications for each patient to be summarized to a total score. The results for the different groups were analyzed using the χ^2-test.

The second scale (Parnas *et al*, 1982) was a 25-item checklist containing a severity weighting (scored 0–4). Each subject was assigned to three global scores: i) frequency score: indicating the total number of pregnancy and birth complications; ii) severity score: representing the weight of the single most severe complication; iii) total score: taking the sum of all recorded and weighted complications experienced by the subject. The scale scores were analysed using the non-parametric Mann-Whitney U-test and the parametric Student t-test in cases of SQRT-error.

Results

Total group of chronically schizophrenic patients

On the "obstetric and birth complication scale" (Lewis and Murray, 1987), 31 of 55 schizophrenics showed a total of 50 complications (table I). In 13 of 20 healthy controls, a total of 20 complications occurred. Thus, the schizophrenic group did not differ from the control group (χ^2 = 0.45, df = 1, ns) on the whole. On the "severity weight allocation scale for specific complications" (Parnas *et al*, 1982) 38 chronic schizophrenics had a total of 83 complications during pregnancy or birth (table II). Eighteen complications occurred in 12 out of 20 normal controls. Compared to the controls, the total schizophrenic group had the same frequency (t = −1.404, ns), severity (t = −0.730, ns), and total score (t = −1.029, ns) of obstetric complications. The OC levels were not correlated to gender.

Familial/sporadic distinction according to DSM III-R

The occurrence of complications during pregnancy and birth was the same in familial and sporadic forms of schizophrenia (χ^2 = 2.40, df = 1, ns, table I) as were frequency (z = 1.058, ns), severity (z = 1.427, ns), and total score (z = 1.350, ns) of obstet-

Table II. Distribution of frequency and severity of obstetric complications, and total scale scores among the diagnostic groups (severity weight allocations scale – Fuchs 1982).

Obstetric complications	*Controls* (n = *20*)	*Total sample* (n = *55*)	*DSM III-R* *Familial* (n = *19*)	*Sporadic* (n = *36*)	*Leonhard criteria* *Unsystematic* (n = *32*)	*Systematic* (n = *23*)
Frequency score	1.00 ± 1.00	1.55 ± 1.62	1.11 ± 1.10	1.78 ± 1.81	1.22 ± 1.31	2.00 ± 1.91*
Severity score	1.50 ± 1.64	1.82 ± 1.68	1.26 ± 1.41	2.11 ± 1.75	1.88 ± 1.81	1.74 ± 1.51
Total score	2.40 ± 2.99	3.40 ± 3.95	2.21 ± 2.80	4.03 ± 4.34	3.37 ± 3.60	3.74 ± 4.47

Leonhard's systematic schizophrenics compared to controls: * $P < 0.1$. No statistically significant differences were found between the other groups. Comparisons were made using Student *t*-test or Mann-Whitney U-test.

ric complications (table II). In addition, both groups were not different from the controls.

Leonhard classification distinguishing between systematic and unsystematic schizophrenia
The occurrence of OCs was the same for both subsamples ($\chi^2 = 0.72$, $df = 1$, ns, table I). As shown in table II, no substantial differences were observed in frequency ($z = 1.522$, ns), severity ($z = 0.090$, ns) and total score ($z = 0.362$, ns) using the Fuchs scale. However, systematic schizophrenics showed a non-significant trend towards an increased frequency of complications in comparison to the controls ($z = 1.799$, $P < 0.1$).

"High genetic risk" group and "low genetic risk" group: (genetic risk supposed to be similar in both classification systems).
Lewis and Murray scale (fig 1): In the *"high genetic risk"* group (schizophrenics who fulfilled the diagnostic criteria of unsystematic schizophrenia and familial schizophrenia), the likelihood of experiencing OCs was significantly less than in the healthy probands ($c2 = 3.99$, $df = 1$, $P < 0.05$). Only three out of 13 mothers reported OCs and none of them reported an infectious disease. The *"low genetic risk"* group (diagnosis of systematic schizophrenia and sporadic schizophrenia) did not have a higher incidence of OCs than controls. However, ten out of 17 mothers reported OCs and there were also seven mothers who reported infections during pregnancy. In five of the seven mothers the infection was followed by further perinatal complications. Fuchs scale (fig 1): The "high genetic risk group" was not different from the controls. In the "low genetic risk" group, there was a non-significant trend towards an increased frequency of complications (infectious diseases were not considered) as compared to normal controls ($z = 1.651$, $P < 0.1$) and the "high genetic risk" group ($z = 1.748$, $P < 0.1$).

Discussion

In order to investigate the incidence of obstetric complications (OCs) in schizophrenia and the relationship of OCs to the development of different schizophrenic sub-types, we interviewed mothers of chronic DSM III-R schizophrenics (APA, 1987) with severe residual states together with normal age-matched controls in a restrospective study. To be included, patients also had to fulfill the diagnostic criteria of Leonhard's systematic or unsystematic schizophrenia (Leonhard, 1979). We used the rating scales of Lewis and Murray (1987) and Fuchs (Parnas *et al,* 1982) which proved to be useful in recording various adverse events in the prenatal, intrapartal and postpartal periods.

In the schizophrenic sample as a whole, the level of OCs showed high parallelity, especially to Parnas' original data of schizophrenic patients (Parnas *et al,* 1982). We failed to find substantial differences in the occurrence of OCs between the "group of schizophrenia", considered as one disease entity, and normal controls (table I and II). These findings are in keeping with the studies of Turner *et al* (1986) and Done *et al* (1991). According to others (Pearlson *et al,* 1985; Nimgaonkar *et al,* 1988; Reddy *et al,* 1990), our results reveal no difference in the presence and severity of perinatal complications between familial and sporadic forms of schizophrenia. The reported increased incidence of OCs in sporadic schizophrenias (Wilcox and Nasrallah, 1987; Schwarzkopf *et al,* 1989; O'Callaghan *et al,* 1990) or in schizophrenias with favourable outcome (Jacobson and Kinney, 1980; Gillberg *et al,* 1986) may be due to different diagnostic samples. All our patients exhibited severe residual psychopathology. Unsystematic schizophrenias according to Leonhard (1979, 1980) did not differ from systematic schizophrenias, but systematic schizophrenias (taking a chronic non-remitting course) showed a non-significant trend towards an increased frequency of complications compared to the controls (table II).

Familial loading with schizophrenic psychoses may not be due to genetic factors and clinical manifestation of the illness may be lacking in predisposed individuals simulating sporadic occurence of the illness. These considerations led us to form a subsample of patients labelled as *"high genetic risk"* and *"low genetic risk"* group whose genetic liability was supposed to be similar in both classification systems.

The *"high genetic risk"* group included patients with diagnoses of unsystematic schizophrenia (mainly genetically determined according to Leonhard) with an obviously positive family history of

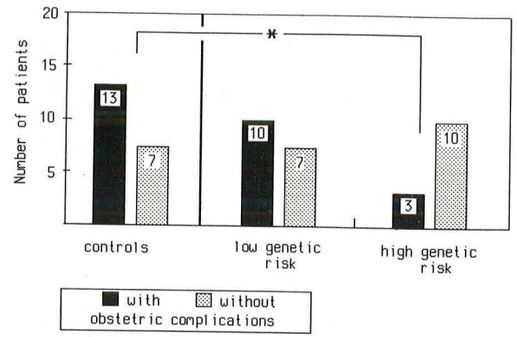

Fig 1. Occurrence of obstetric complications in "low and high genetic risk" groups. Subsample of patients ($n = 30$) with an equal genetic risk in familial/sporadic concept in DSM III-R and unsystematic/systematic distinction in Leonhard classification: The "low genetic risk" group comprises patients ($n = 17$), who fitted the definition of systematic schizophrenia according to Leonhard and sporadic schizophrenia in DSM III-R. The "high genetic risk" group ($n = 13$) represents patients who fulfilled the criteria of Leonhard's unsystematic schizophrenia (mainly genetically determined according to Leonhard's findings) and of familial schizophrenia in the DSM III-R. This group of "high genetic risk" suffered significantly less from obstetric complications than did controls in the Lewis and Murray scale ($P < 0.05$; $df = 1$; $\chi^2 = 3.99$).

schizophrenia. Here, the frequency of OCs was similar to the controls, but the number of patients who experienced OCs was significantly less compared to the controls (fig 1). In addition, no mother of these patients had suffered from an infectious disease during gestation, as previously reported (Stöber *et al,* 1992). This is in contrast with Parnas *et al's* (1982) assumptions that, among individuals with supposed genetic vulnerability, those with uncomplicated births develop schizotypal personality disorder or remain non-schizophrenic and those with OCs have a high risk of developing schizophrenia. Our results likewise contradict the "two strike" hypothesis which assumes an interaction of genetic predisposition and prenatal and/or perinatal environmental stressors in the etiology of schizophrenia (Parnas *et al,* 1982; Machon *et al,* 1987; Roberts, 1991; Bracha *et al,* 1992). As opposed to this, we found evidence that genetic influences are sufficient etiological factors for psychotic breakdown in sub-populations with manifest genetic risk. Obstetric complications and maternal infections during pregnancy are scarcely reported in the *"high genetic risk"* group with presupposed strong heredity in both classification systems (fig 1). The significantly lower incidence of complications in this group may be an indication of an increased sensitivity to fatal perinatal damage. Several authors (Rieder *et al,* 1975; Hanson *et al,* 1976; Wrede *et al,* 1980; Modrewsky, 1980; Watson *et al,* 1987) reported an increased fetal and perinatal mortality among the offspring of schizophrenic mothers. Beckmann and Franzek (1992) and Franzek and Beckmann (1992) found a tendency for births of schizophrenics with high familial loading to decrease in a defined winter and spring period. Our results provide indirect support for their hypothesis, that, in some fetuses at high genetic risk, additional environmentally noxious agents exaggerate the level of perinatal death.

The *"low genetic risk"* group comprised patients with systematic schizophrenia (mainly environmentally determined according to Leonhard) and with a negative family history of schizophrenia (sporadic forms). This group was associated with a non-significant trend towards an increased frequency of OCs compared to controls and the "high genetic risk" (fig 2). The "low genetic risk" group as well as Leonhard's systematic schizophrenias were also highly significantly associated with maternal infectious diseases during the second trimester of gestation (Stöber *et al,* 1992). In the group at "low genetic risk", five of the seven mothers, who reported an infectious disease during this period, had further perinatal complications. On

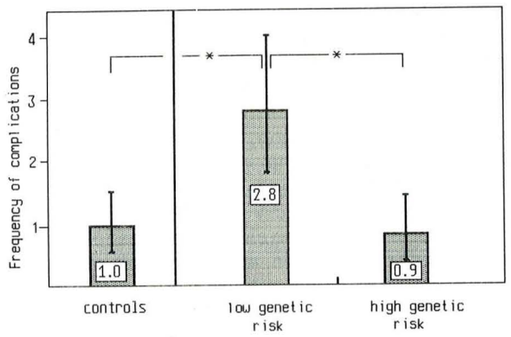

Fig 2. Frequency of obstetric complications in "low and high genetic risk" groups. Subsample of patients ($n = 30$) that had an equal genetic risk in both the DSM III-R and the Leonhard classification. The "high genetic risk" group represents unsystematic schizophrenics with a positive family history of schizophrenia. The "low genetic risk" group comprised Leonhard's systematic schizophrenics (mainly environmentally determined according to Leonhard) with a negative family history of schizophrenia. The patients with obviously "low genetic risk" showed a statistical trend towards a heightened frequency of obstetric complications compared to normal controls and to the "high genetic risk" group in the Fuchs scale ($P < 0.1$; $z = 1.651$; $z = 1.748$).

the one hand, obstetric complications could be independently noxious events which intensify disturbances caused by mid-gestational infections. On the other hand, severe maternal infectious diseases could increase the likelihood of perinatal complications and, thus, be responsible for the heightened level of OCs in the group at "low genetic risk" and in Leonhard's systematic schizophrenias.

The coincidence of maternal infections during mid-gestation and perinatal damage seems to increase the risk of developing chronic, non-genetic schizophrenia in the affected children. Maternal infections are supposed to be important factors for the deviations of prenatal brain maturation (Jakob and Beckmann, 1986; Mednick *et al,* 1988). Definite cytoarchitectonic deviances in para-hippocampal gyrus that were found in post-mortem brain studies of schizophrenic patients are explained by a disruption of neuronal migration during mid-gestation (Jakob and Beckmann, 1986; Beckmann and Jakob, 1991; Arnold *et al,* 1991). Serious obstetric complications point to abnormal cerebral oxidative metabolism and to intrapartum hypoxic-ischaemic episodes (Hill, 1991; Roth *et al,* 1992). Anoxia-induced brain damage leads additionally to structural disorganization, loss of cell connectivity and selective cell death (Janowsky and Finlay, 1986).

This study gave rise to the following conclusions: i) in schizophrenias with a low genetic risk, perinatal complications may be of some etiological importance, and ii) in schizophrenias with high genetic risk, obstetric complications do not essentially contribute to the etiology of the disease.

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