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Obstetric complications predict treatment response in first-episode schizophrenia

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ABSTRACT

Background. Understanding the role of obstetric complications (OCs) in schizophrenia could potentially shed light on the heterogeneity in the aetiology and course of schizophrenia. Many investigators have reported an association between OCs and schizophrenia, but few have examined the association between OCs and treatment outcome. We investigated this question in a sample of patients studied during their first episode of schizophrenia, schizoaffective or schizophreniform disorder.

Method. OC histories were obtained for 59 patients participating in the Hillside First Episode Study. Cox proportional hazards regression analysis was used to estimate the effect of OCs on treatment response during the first episode of schizophrenia.

Results. Twelve of the 59 patients (20%) had positive histories of OCs. This group exhibited lower rates of treatment response than those with negative OC histories (hazard ratio controlling for sex = 0·28; 95% CI = 0·13, 0·62). The positive OC group also had significantly greater lateral ventricle volume, baseline disorganization and number of live births. The effect of OC history on treatment response held when these three variables were controlled for.

Conclusion. A history of obstetric complications predicted poor response to treatment in the first episode of schizophrenia. This large effect was based on a small sample of 59 patients. Thus, replication is called for.

INTRODUCTION

Numerous studies have examined the association between obstetric complications (OCs) and schizophrenia. The majority have found that subjects exposed to OCs are at greater risk of developing schizophrenia. A meta-analysis of 21 case–control and three cohort studies (Geddes & Lawrie, 1995) indicated that the odds of developing schizophrenia were doubled by exposure to OCs. Our group failed to find differences in the occurrence of OCs between schizophrenia, affective disorder and normal comparison groups (Gunduz *et al.* 1997). Murray *et al.* (1985) suggested subdividing patients with schizophrenia into 'familial' and 'non-familial' cases as a crude first step towards aetiological classification, with OCs playing a role in environmentally induced brain damage. The history of OCs could potentially shed light on the heterogeneity in both the aetiology and course of schizophrenia. However, we found only three studies that have looked at the association between OCs and illness outcome in schizophrenia.

Wilcox & Nasrallah (1987) examined 511 patients who had been diagnosed with schizophrenia during the initial episode. Re-diagnosis of these patients using Feighner criteria (Feighner *et al.* 1972) resulted in 311 patients being classified as 'good prognosis', with diagnoses of schizophreniform or schizoaffective disorder by DSM-III criteria. The remaining 200 cases were classified as chronic schizo-

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phrenia. History of perinatal insult, obtained from detailed medical histories, was present in 42 (21%) of the 200 patients with chronic schizophrenia compared to 42 (13·5%) of the 311 good prognosis patients ($\chi^2 = 3{\cdot}90$, $P < 0{\cdot}05$).

Nimgaonkar and his colleagues (1988) studied 53 consecutive admissions for schizophrenia to the Maudsley Hospital between October 1985 and June 1986. These patients had a mean age of 32 years and a mean of 2·9 admissions. Obstetric histories were obtained from case records and interviews with close relatives. OCs were rated as absent, equivocal or definite (Lewis *et al.* 1989). OCs were identified as definite in 11 patients and absent in 25 patients. The 11 patients with definite OC histories and the 25 with normal histories did not differ in the change from baseline to 6 weeks after therapy in total symptom scores, measured using the Schizophrenia Scale of Montgomery *et al.* (1983). Patients were classified into responders (> 80% improvement in total symptom scores) and non-responders (< 20% improvement). Two of 17 responders (11·8%) had definite OC histories compared to five of 18 non-responders (27·7%). Thus, the odds of a non-responder having a definite OC history was 2·89 (95% confidence interval (CI) = 0·48, 17·5) times greater than for a treatment responder. This difference was however not statistically significant.

Smith and his colleagues (1995) studied 83 consecutive admissions for schizophrenia for whom obstetric histories could be obtained using semi-structured interviews with the patients' mothers. OCs, rated according to the scale of Lewis and colleagues (1989), were definitely present in 40 (44%) of the 83 patients, equivocal in 14 (16%), and absent in 36 (40%). These patients tended to be severely ill, with most being admitted due to poor treatment response. The mean (S.D.) duration of illness was 9·7 (7·9) years for the group with definite history of OCs and 7·1 (5·0) years for the group with no history of OCs. The definite and no history groups did not differ in their response to treatment.

The lack of a significant difference in treatment outcome in the Nimgaonkar and Smith studies could be due to the chronicity and severity of disease in these two samples. The Nimgaonkar study suggests that the odds of definite OCs are greater in the group with poor treatment response. The evidence offered by Wilcox and Nasrallah that perinatal insult occurs more frequently in the poor prognosis group is indirect because there was no analysis which linked individual OC status to treatment response. While the rate of recovery was greater for the good prognosis group, 46% of this group did not recover.

We investigated the effect of OCs on the treatment response of patients during the first episode of schizophrenia. Studying patients admitted for their first episodes of illness eliminates the bias of including mainly chronic and severely ill patients. These first episode patients provide sufficient variability in treatment response to directly relate individual treatment outcome and OC history.

METHOD

Patients in their first episode of schizophrenia were ascertained as part of the Prospective Study of Psychobiology of Schizophrenia at Hillside Hospital, the methods and results of which have previously been reported (Lieberman *et al.* 1992, 1993*a*, *b*). This study was conducted using the guidelines of the Institutional Review Board of the Long Island Jewish Medical Center. Written informed consent was obtained from the patients recruited into the study and from the mothers who provided obstetric histories. Signed releases for birth and hospital records were obtained from the families. Collection of obstetric histories was an add-on project funded by a small grant to Dr Degreef. Histories of OCs were obtained for 59 patients (34 males and 25 females). This group was a subset of 118 patients who were initially treated with standard antipsychotic drugs. The majority of the histories was obtained from the prospective study's earlier participants during the add-on study's active funding period, with 40 histories obtained from the 58 study subjects who had entered the study prior to 1990. Histories were based on mother's recall alone in 26 (44%) of the patients and supplemented with birth records in the rest of the sample. Patients were grouped *a priori* according to whether or not they had a history of any Level 5 OC (clearly potentially greatly harmful; e.g. early bleeding, very prolonged labour, asphyxia) according to the McNeil–Sjöström Scale for OCs (McNeil *et al.* 1994).

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Patients were treated openly according to a standard algorithm, initially receiving fluphenazine up to 20 mg/day. Patients who did not respond after 6 weeks had their dose increased to 40 mg/day for an additional 4 weeks. Patients who did not respond to fluphenazine were switched to haloperidol 20 mg/day for 6 weeks and raised to 40 mg/day for 4 additional weeks if needed. Lithium was added to haloperidol if patients were still unresponsive followed, if needed, by a trial of either molindone up to 300 mg/day or loxapine up to 150 mg/day. Patients who remained treatment resistant were then treated with clozapine up to 900 mg/day.

Psychopathology was evaluated using the following instruments: Schedule for Affective Disorders and Schizophrenia Change + Psychosis and Disorganization Scale (SADS-C + PD; Spitzer & Endicott, 1978); Scale for Assessment of Negative Symptoms (SNAS; Andreasen, 1983); and the Clinical Global Impression Scale (CGI; Guy, 1976). Patients were rated bi-weekly during acute treatment on the SADS-C + PD and CGI and considered treatment responders when they achieved no rating > 3 (mild) on SADS-C + PD psychotic symptom items, CGI severity rating $\leqslant 3$ (mild), and CGI improvement rating of 2 (much improved) or 1 (very much improved). In addition, this improvement was required to persist for 8 weeks. Measures of symptomatology at baseline included hallucinations and delusions (mean of SADS-C + PD severity of hallucinations and delusions items), disorganization (mean of SADS-C + PD formal thought disorder (impaired understandability, derailment, illogical thinking), inappropriate affect, and bizarre behaviour items) and negative symptoms (mean of SANS affective flattening, alogia, avolition/apathy, and anhedonia/asociality global items). History of schizophrenia in first-degree relatives was ascertained from a close relative, usually a parent, using the Family History – Research Diagnostic Criteria (Endicott *et al.* 1978).

Coronal magnetic resonance images were acquired on a Siemens Magnetom operating at 1.0 tesla using fast low-angle-shots, gradient-refocused, 3-dimensional sequence with a 50° flip angle, 40 ms repeat time, 15 ms echo time, and 63 contiguous 3·1 mm slices. Regional volumes were measured using a semiautomated, computerized system (Ashtari *et al.* 1990).

The statistical tests for between group comparisons included χ^2 tests, *t* tests, and analysis of variance. The effect of a history of Level 5 OC on treatment response during the first episode of schizophrenia was estimated using Cox proportional hazards regression analysis. Survival analysis is appropriate for the analysis of treatment response because some patients still had not responded to treatment either due to recent study entry or long duration of acute treatment. Cox proportional hazards regression allows the use of covariates in the analyses. We tested for non-proportionality of hazards, a deviation from the statistical assumptions of Cox models, using analyses which included interactions of the OC history variable with the natural logarithm of time.

RESULTS

The 59 study subjects included 34 males and 25 females. An examination of the course of illness revealed no differences in outcome between the patients who were included in these analyses and the patients who did not have obstetric history data. The 59 patients were followed in the study for a mean of 225 weeks (S.D. = 99; range = 47–460). Forty-three (73%) of the patients had an RDC diagnosis of schizophrenia (32 paranoid, eight undifferentiated, two disorganized and one catatonic) while 16 (27%) were diagnosed as schizoaffective (13 depressed, three manic). The racial composition of the sample was 28 (48%) White, 18 (31%) Black, eight (14%) Hispanic, three (5%) Asian and two (3%) Other. Forty-eight (81%) had never married, five (9%) were currently married and six (10%) were separated or divorced. Familial social class was upper for six (10%), upper middle for 15 (26%), middle for 17 (29%), lower middle for nine (16%) and lower for 11 (19%). Fifty patients (91%) of the 55 patients with available gestational age were born full-term while two patients (4%) were born at less than 33 weeks gestation. Five (9%) of the patients had a history of schizophrenia in first-degree relatives. Table 1 lists additional demographic and clinical characteristics of the sample.

Twelve of the 59 patients (20%) had positive histories of Level 5 OCs. These complications included four with prolonged labour, two each with emergency C-section, early bleeding and

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Table 1. *Characteristics of sample*

	Mean	(S.D.)	Range
Characteristics of patients			
Age at study entry	23·8	(6·2)	14–39
Weeks of psychiatric Sx prior to entry	132	(159)	1–676
Weeks of psychotic Sx prior to entry	39·5	(56·0)	1–260
Age of onset of psychotic Sx	23	(6·1)	11–39
Baseline symptomatology			
Hallucinations and delusions	4·6	(1·1)	1·5–6
Disorganization	2·6	(1·2)	1–5·3
Negative symptoms	2·8	(1·0)	1–5
Characteristics of mothers			
Age at birth of patient	28·6	(5·9)	14–41
Number of pregnancies	2·7	(1·9)	1–8
Number of live births	2·5	(1·6)	1–7

<33 weeks gestation, and one each with smoking two packs a day and syphilis, both during the third trimester. The child of one of the mothers who underwent an emergency C-section also experienced foetal distress and exhibited meconium stain. One mother who underwent prolonged labour also had attempted an abortion in the first trimester.

The proportion of patients with positive histories was greater among women (28%) than among men (15%) although this difference was not statistically significant. The proportions of positive OC histories were similar between schizophrenic (21%) and schizoaffective groups (19%). The racial groups had similar proportions of positive OC histories (18% in Whites, 22% in Blacks, 25% in Hispanics and 20% in the combined Asian and Other group). The proportions of patients with histories of schizophrenia in first-degree relatives were 9% in the negative OC group and 8% in the positive OC group.

Table 2 compares clinical characteristics of patients as well as maternal characteristics by OC history. The mean size of the lateral ventricles was almost a third larger in the positive OC group, in spite of the larger proportion of women with positive OC histories. The positive OC group had more disorganization symptoms at baseline, with a mean of 3·2 (slightly above mild) compared to 2·4 (between slight and mild) in the negative OC group. The mothers in the positive OC group had significantly fewer pregnancies and consequently significantly fewer live births compared with the mothers in the negative OC group. There were no differences in age, age of onset of psychotic symptoms, duration of psychotic symptoms prior to study entry, baseline levels of hallucinations and delusions as well as negative symptoms, and age of the mother when the patient was born. Because the positive OC group had a larger proportion of females, we compared age and age of onset of psychotic symptoms separately for males and females. These separate analyses revealed similar age and age of onset in the groups with and without OCs.

Fig. 1 shows the cumulative rate of treatment response in positive and negative OC history

Table 2. *Selected characteristics by history of obstetric complications*

	No Hx of OCs		Positive Hx of OCs	
	Mean	(S.D.)	Mean	(S.D.)
Characteristics of patients				
Age at study entry	23·8	(6·0)	23·8	(7·4)
Age at onset of psychotic Sx	23·0	(6·0)	23·0	(6·9)
Weeks of psychotic Sx prior to entry	39·1	(58·2)	41·1	(48·7)
Lateral ventricle volume(cc) ($P < 0·01$)*	16·7	(6·7)	22·1	(6·0)
Baseline symptomatology				
Hallucinations and delusions	4·6	(1·2)	4·9	(0·8)
Disorganization ($P = 0·055$)	2·4	(1·2)	3·2	(1·1)
Negative symptoms	2·9	(0·9)	2·7	(1·0)
Characteristics of mothers				
Age of mother at birth of patient	28·7	(5·7)	27·9	(6·8)
Number of pregnancies ($P < 0·01$)	3·0	(2·0)	1·8	(0·9)
Number of live births ($P < 0·01$)	2·8	(1·7)	1·6	(0·7)

* P value controlling for sex.

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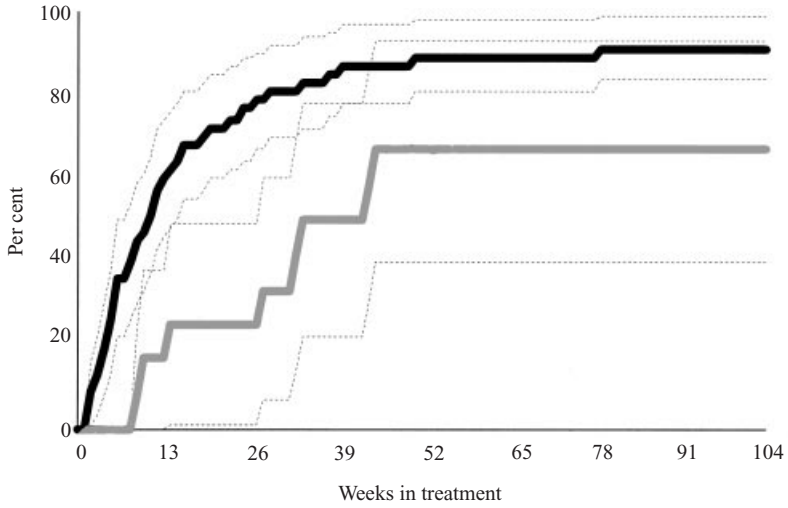


FIG. 1. Cumulative percentage of patients responding to treatment during their first episode of treatment. The black (upper) curve represents the group with no history of potentially seriously harmful obstetric complications ($N = 47$) and the grey (lower) curve represents the group with positive history of potentially greatly harmful obstetric complications ($N = 12$). The dashed lines represent 95% confidence limits.

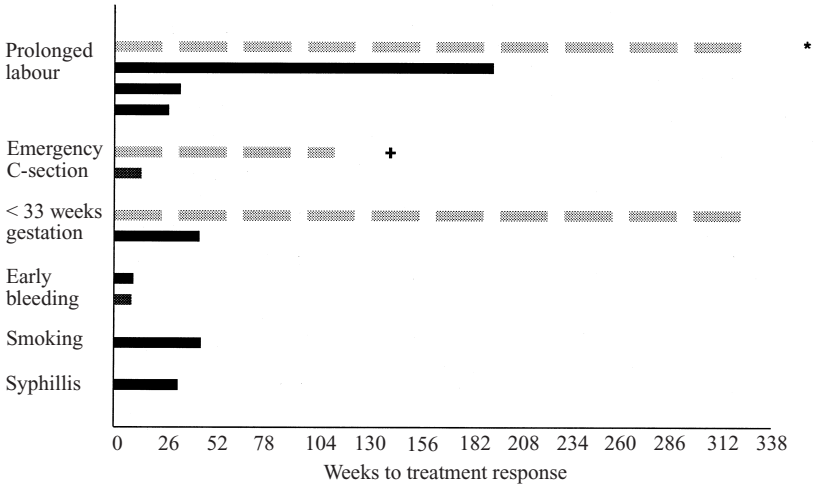


FIG. 2. Time to treatment response for 12 patients with histories of obstetric complications by specific complication type. The grey dashed bars represent three patients who did not respond to treatment. (*, Indicates a patient whose mother also had attempted an abortion in the first trimester; +, a patient who also had foetal distress and meconium stain.)

groups. The median time to treatment response was 11 weeks (95% CI = 8, 15) in the group of patients without Level 5 OCs and 39 weeks (95% CI = 28, 195) in the positive OC group. Six patients had not responded to treatment during their last observation point, including three in the positive OC group who were last seen at 83, 246 and 319 weeks and three in the negative OC group who were last observed at 113, 323 and 327 weeks. Cox proportional hazards regression analysis was performed with treatment response as the outcome variable and sex as a covariate due to association of sex with both treatment outcome and history of OC in our sample. The positive OC group exhibited lower rates of treatment response compared to the group with negative histories (hazard ratio controlling for sex = 0·28; 95% CI = 0·13, 0·62).

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Three variables which differed between OC groups, namely lateral ventricle volume, baseline disorganization and number of maternal live births, also had at least trend level associations with treatment outcome. The hazard ratio barely changed (0·29; 95% CI = 0·12, 0·73) with the addition of these three covariates into the Cox regression model.

An analysis limited to the 33 patients who had available birth records was performed in order to minimize the potential of biased maternal recall. The hazard ratio was 0·30 (95% CI = 0·12, 0·79). The effects of OCs were similar in the 40 patients who had entered the study prior to 1990 and the 19 patients who entered subsequently (hazard ratios of 0·26 and 0·37 respectively). Sensitivity analyses in the pre-1990 cohort which assigned OC histories to the 19 patients with missing OC data resulted in hazard ratios of 0·29 when missing was coded as negative and 0·54 when missing was coded as positive. These hazard ratios were still significantly different from unity while not significantly different from each other.

The individual times to treatment response for the 12 patients with level 5 OCs are shown in Fig. 2, grouped by specific complications. While the median time to recovery for the 47 patients who did not have Level 5 OCs was 11 weeks, only two of the 12 positive OC patients responded to treatment earlier than 11 weeks. These two patients both had mothers who had early bleeding. Aside from the relatively benign effects in these two patients, there is no clear pattern as to the contribution of specific complications. One patient who had not responded to treatment after 327 weeks had a history of prolonged labour and an attempted first trimester abortion. A patient who had not responded to treatment after 113 weeks had a history of emergency C-section and foetal distress.

DISCUSSION

Our major finding is that exposure to potentially seriously harmful OCs strongly predicts poorer response to treatment in the first episode of schizophrenia. The association between OCs and other measures of illness severity, particularly measures of brain pathomorphology, has previously been reported (Owen *et al.* 1988; Silverton *et al.* 1988; Cannon *et al.* 1993). We, likewise, found larger lateral ventricles and more symptoms of disorganization at study entry in the positive OC group. If the effect of OCs were mediated mainly by ventricular size and disorganized symptoms, we would expect their inclusion in the Cox regression models to reduce or eliminate the effect of OCs. However, the effect of OCs on treatment response was statistically independent of the effects of enlarged lateral ventricles and increased disorganization. One explanation for the inability to account for the OC effect could have been due to relatively lower reliability of the measures of lateral ventricle volume and disorganization. However, this is unlikely because ventricular volume is a highly reliable measure with intraclass correlations (ICC) of 0·94 to 0·99 for ventricular regions (Ashtari *et al.* 1990). Similarly, ICCs for the items included in the disorganization scale range from 0·80 for illogical thinking to 0·98 for bizarre behaviour. Combination of the five SADS-C + PD items measuring formal thought disorder, inappropriate affect and bizarre behaviour would enhance the reliability of the disorganization scale (Cronbach, 1951). The statistically independent effect of OCs on treatment response suggests some other deleterious neurobiological insult or insults, aside from the already measured ventricular enlargement and disorganized symptoms, which compromises the patient's capacity for treatment response and recovery. We could expect to shed more light on these unmeasured insults as we refine our measurement techniques.

Patients with and without histories of schizophrenia in first-degree relatives did not differ in OCs in our study. This result does not support a simple taxonomy, which contrasts genetic factors *versus* environmentally induced brain damage, but rather points towards a more complex web of aetiological factors.

Treatment response varied within the positive OC group. With only 12 patients exposed to potentially seriously harmful OCs, it is difficult to discern a pattern as to whether there are specific complications that exert effects on treatment response. The heterogeneity of the OC effect on treatment response could be due to variability in obstetrical insults, as well as in the mediating processes by which structures other than and/or in addition to those whose pathology is reflected by ventricular volume and

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disorganized symptoms are affected. OCs thus represent a set of various neurobiological insults that contribute to the potential severity of a patient's illness either independently or in conjunction with other aetiopathogenic factors (e.g. genetic).

Because the large effect of OC history on treatment response was based on a small sample of 59 patients, replication of our results is necessary before definitive conclusions can be made regarding obstetric complications and the course of schizophrenia. The necessity of a larger sample is amplified by the heterogeneity in the mix of obstetric complications that could potentially affect the course of schizophrenia. The new generation of antipsychotic agents had been heralded for greater efficacy among treatment-resistant patients as well as a smaller risk for developing extrapyramidal side effects. Since the patients in our study were treated with the older generation of antipsychotic drugs, it is of interest whether the relationship between OC history and treatment response will hold among patients treated with the new generation of neuroleptic drugs.

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