A Sex-Specified Effect of Obstetrical Complications in Symptoms of Schizophrenia

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Abstract

Research on obstetrical complications (OCs) reports a connection with the development of more severe (negative) schizophrenic symptoms. To date, no study has tested to see if this association varies by sex. A large sample (n=786) of patients from a state hospital population in the United States was screened for study variables. Statistical tests employed were crosstabular analysis and analysis of variance. The central finding is a significant connection between OCs and negative symptoms for females but not for males. The authors speculate that there may be differences in the ways by which male and female fetuses respond to OCs or a distinction between the sexes in genetic predisposition toward severe schizophrenia.

Key Words: Schizophrenia, Gender Differences, Obstetrical Complications, Positive Symptoms, Negative Symptoms

Introduction

Obstetrical Complications and Schizophrenia

Obstetrical complications (OCs) are a regularly reported correlate of schizophrenia (1-3). Numerous studies with different types of designs and samples report that deviations from the normal course of pregnancy are associated with adult schizophrenia in offspring (4-7). The first hint of a connection between birth complications and schizophrenia occurred in the early twentieth century. Since then, research on OCs and schizophrenia has focused on the role of low birth weight, studies of high-risk groups, brain imaging studies, case-control studies, and population-based studies (8).

Since OCs can potentially damage the brain during pregnancy or delivery (9, 10), they may be more common in schizophrenic patients with early age of onset. This hypothesis is based on the expectation that brain injuries are not likely to remain latent for extended periods of time. Indeed, a meta-analysis based on the data of eleven research groups indicates that schizophrenic patients with early onset are much more likely than their later-onset counterparts to have had their gestation or birth complicated by an OC (11).

Regardless of age of onset or severity of symptoms, patients with schizophrenia are clearly more likely to show a history of OCs than control subjects. In fact, Preti et al. (12) report that schizophrenic patients are five times more likely to have suffered an antecedent OC of a severe nature than are normal “healthy” people with very similar birth characteristics. And three population-based studies conducted within a Sweden-wide cohort of all children born during 1973–79 report that adverse perinatal events are more strongly associated with schizophrenia than with any other form of psychosis (13). The few studies that failed to substantiate a relationship between OCs and the later development of schizophrenia used unique methodologies, which are difficult to compare with results from other studies (3).

The types of OCs investigated by different studies are wide and varied. Byrne et al. (14) show that increased risk for schizophrenia is associated with prematurity, manual

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**Clinical Implications**

It has been established that obstetrical complications (OCs) are associated with brain damage. This, in turn, has a role in the pathogenesis of some cases of schizophrenia (9). There is also literature linking brain abnormality with negative symptoms, a presentation of schizophrenia with poor prognosis (18, 19). The central finding of the present study further pinpoints the connection between OCs and negative symptomatology. Specifically, we find that the connection is present for females and not for males. What is the underlying basis for this gender-specific phenomenon? We offer two hypothetical explanations: first, our finding may connect with studies reporting that the male fetus is more fragile than the female fetus. Consequently, an OC may be more likely to prevent birth among males in the first place, whereas a similar insult to a female fetus may not result in spontaneous abortion but rather life with a brain abnormality. Simply stated, the males are more likely to die and the females are more likely to end up being psychotic.

The second hypothetical explanation for our gender-specific finding of the connection between OCs and negative symptomatology is not inconsistent with the fact that the male fetus is more fragile. In fact, it is an independent interpretation. We hypothesize that there may be separate etiologies of negative symptoms for male and female schizophrenics. One causal route may be genetic and the other may be obstetrical. As suggested in this study, the causal route for females is an insult to the fetal brain inflicted by OCs. Other researchers suggest that negative symptoms in men stem from a greater biological vulnerability caused by stronger genetic penetrance (54). Clearly, there is much more research needed to untangle the complex interplay of gender, genetics, and OCs in the genesis of schizophrenia with negative symptoms.

The vast majority of people with OCs do not develop schizophrenia, and OCs are neither necessary nor sufficient causal factors for schizophrenia and should instead be described as component causes (16). Regardless of the nature and degree of their causal links with schizophrenia, OCs clearly provide an additional factor that should be taken into consideration when identifying risk factors for this psychosis (4).

**Obstetrical Complications and Negative Symptoms**

If OCs have the potential to cause brain damage, is it possible that OCs connect with negative symptomatology? Indeed, schizophrenia with negative symptoms—a condition connected with poor prognosis and diminished responsiveness to medications compared to schizophrenia with positive symptoms—has been linked with an abnormality in the actual structure of the brain (18, 19). This is a compelling reason why negative symptomatology is included as a major variable in this study. Here we refer to type of schizophrenia in two ways, according to types of symptoms: negative form and positive form. To date, there has been a paucity of studies examining type of schizophrenia and OCs (20). Our recent research has been an exception in that regard. We analyzed data from a large sample (n=437) of patients from a state hospital population in the U.S. and found a significant association between OCs and negative symptoms, but only for patients from a lower social class of origin (21).

**Gender and Symptoms of Schizophrenia**

Numerous studies have tested for gender differences in symptoms of schizophrenia. A majority of those studies report that male schizophrenics are more likely to manifest negative symptoms than their female counterparts who have higher rates of positive symptoms (22-24). Leung et al. (25), in a review of the literature on gender differences in schizophrenia, reached the conclusion that males show more negative symptoms (such as social withdrawal, blunted affect, poverty of speech, and amotivation) with greater structural brain and neurophysiological abnormalities. Related assessments of gender differences in symptomatology also report greater severity of negative symptoms among males (26) as well as poor outcome (27, 28).

While a majority of studies report a greater propensity for negative symptoms among male schizophrenics, there are also contradictory findings of no significant differences in symptomatology between male and female patients (29, 30). It is important to note, however, that gender differences may not be entirely due to biological factors alone. Social and cultural factors play a significant role in the expression of negative symptoms and may account for some of the observed differences.
This is an interesting fact because it leads to the question of possible intervening variables that may produce the sex difference in symptoms. Indeed, our earlier research uncovered a reduced risk for negative symptoms among males born into nonpoor families (21). In that study, social class of origin and gender were co-associated with type of schizophrenia. Clearly, gender differences in schizophrenic symptoms are based on factors that are not fully understood. In fact, research to date begs for investigations of previously unexamined interconnections. This study is a response to that call.

The major hypothesis of the present study is that there is a significant association between OCs, schizophrenic symptoms, and gender. This study is unusual because it simultaneously examines the interaction of OCs and symptoms with gender. Other researchers have looked at the relationship between symptoms of schizophrenia and gender (20, 21), but this is the first study to test for an association between those two variables and OCs.

**Methods**

Data for this study have been taken from the cumulative anonymous medical records of 786 schizophrenic patients discharged from Norristown State Hospital (NSH) in Pennsylvania (United States) between 1984 and 1990. Diagnostic procedures employed multidisciplinary evaluations with periodic review. Specific criteria for index diagnosis are based on the Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM) (31).

Upon admission, patients were evaluated by staff psychiatrists and other members of a multidisciplinary team within forty-eight hours for diagnosis and treatment plan purposes. Later, diagnostic reviews were conducted for each patient every three months, or as needed, during hospitalization. Since some patients have been discharged and readmitted over time, we employed a combination of three operational measures to enhance longitudinal analysis of symptom stability. The measures included clinical assessments by NSH staff at intake and during last hospital stay, as well as DSM diagnosis at last discharge.

**Clinical Assessments**

In addition to diagnosis by DSM standards, NSH staff professionals further categorized patients into negative (e.g., symptoms such as mutism) and positive (e.g., symptoms such as hallucinations) subtypes. Subtyping is based on diagnosticians’ judgments of clear presentation of positive or negative features at intake and during last hospital stay. Classification into these subtypes is based on positive and/or negative features of many individuals with schizophrenia (32). It is also compatible with research centering on “deficit/nondeficit schizophrenia.” Deficit schizophrenia is an older terminology used to describe long-term patients with a persistent negative presentation. The division of schizophrenia into either “deficit/nondeficit” or “negative/positive” subtypes has yielded many important substantive findings about schizophrenia (33-35). Subtyping in this study is enhanced by chart materials with detailed patient symptomatology.

In addition to subtyping drawn from patient files, a number of positive and negative scales have been retrospectively applied from chart materials. They include the Scale for the Assessment of Negative Symptoms (SANS) (36), the Scale for the Assessment of Positive Symptoms (SAPS) (36), and the Positive and Negative Syndrome Scale (PANSS) (37). Although some may question the validity and reliability of chart-based assessments of negative and positive symptoms, we do not think these are serious problems in this study. It was standard procedure at NSH to require that interviewer observation of the patient be completely and directly recorded onto the charts. Therefore, the clinical assessments were solely conducted by NSH staff professionals, and we retrospectively applied the identical assessments to our sample. Both the original assessments at NSH and our replication of those assessments were conducted independently of patient history of OCs. The literature reports that the retrospective application of the SANS, SAPS and PANSS can be completed from chart materials if the latter are sufficiently detailed (38, 39). Such was the case in the present study.

One of the issues we faced was how to deal with diagnoses that changed over time. This proved to be a minor problem, since this type of discrepancy rarely occurred and, when it did occur, we simply eliminated the case from the sample. Thus, diagnosis is operationalized from three temporal sources: clinical assessment at first intake, during last hospital stay, and DSM diagnosis at last discharge. The temporal points of these measurements not only permit the observation of symptom stability over time, but also reflect studies cited earlier that schizophrenia patients who show persistent negative symptoms are an important subgroup with low-remission rates (40-44).

Negative/positive assessments were conducted by three independent raters. Two of the raters are experts in the field; one is a clinical psychologist and the other is a psychiatric sociologist. Consensus was reached on the classification of all included cases. Thus, interrater reliability is one hundred percent because, in the rare instances where there was disagreement, the cases were dropped. We also eliminated cases in which extrapyramidal complications were present.

As noted above, patients who did not clearly present as negative or positive were not included in this study. Individuals who had both positive and negative symptoms were
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excluded. Thus, a patient was cross verified as negative only if chart materials reflected presentation of negative symptoms at first admission and during the last hospital stay and the index diagnosis was DSM “chronic” at discharge.

**Obstetrical Complications**

Like socioeconomic status (SES), data about OCs were obtained from the “social history” section of the hospital records. Nine obstetrical complications appeared in these accounts: maternal health problems during pregnancy, prenatal alcohol abuse, prenatal drug abuse, prenatal violence, premature birth, unusually long labor, breech birth, forceps delivery, and other delivery complications. Each OC was rare, almost always in single digit percentages; this rendered statistical tests of any particular complication untenable.

Prevalence of obstetrical complications was probably underestimated in the social histories due to recall problems since, by the time of admission, several decades would have elapsed since the patients were born. Obstetrical histories were provided by first-degree relatives, which usually, but not always, included the patient’s mother. There was an interview format which included questions about OCs. Studies of the effect of maternal recall bias of OCs in research on schizophrenia have produced mixed results. One study suggested that schizophrenic patients had higher rates of OCs recalled by their mothers than controls (45). Another study found no evidence of positive recall bias as mothers of offspring with schizophrenia reported fewer complications than indicated on their obstetric records (46). Additionally, there is no reason to believe that recall bias in the present study will differentially affect the other variables (sex and symptomatology) in the research model to produce misleading effects.

**Data Analysis**

Type of schizophrenia, the dependent variable in the present model, is coded as a simple dichotomy such that 0=positive and 1=negative schizophrenia. The other variables in the model are sex of patient and, of course, obstetrical complications as the independent variable. Each of the nine complications identified above were relatively rarely reported events, so straightforward indexing—i.e., just adding up the number of OCs per patient—turned out to be fruitless because multiple OCs were too rare to permit meaningful statistical testing.

Therefore, two different breakdowns of OCs are utilized in the successive stages of analysis. The first separates patients with at least one OC in their social histories from those with none. This is the version of the independent variable for crosstabular analyses. Stage two of the analysis will employ analysis of variance (ANOVA) to facilitate direct testing of statistical interaction not available in crosstabula-

tion. For the ANOVA test, the OC breakdown will be none, one and two or more reported OCs rather than a complete indexing for the reason offered above. Calculations are performed using the MicroCase data analysis system.

**Results**

**Crosstabular Analysis**

Table 1 displays the crosstabulation of obstetrical complications by schizophrenic subtype for males in the sample. Observe that in the top row—labeled “No,” meaning no OCs—the prevalence of negative symptoms is 29.3%. In the “Yes” row—indicating that at least one OC is in the patient’s background—the comparable percentage is 28.7%. Given the nearly identical percentages of the top and bottom rows, there is no surprise that the chi-square test yields no evidence of effect ($X^2=0.017, p=.897$). For sample males, OC history is unrelated to type of schizophrenia.

<table>
<thead>
<tr>
<th>Type of Schizophrenia by Obstetrical Complications for Males</th>
<th>Type of Schizophrenia</th>
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<tbody>
<tr>
<td>Obstetrical Complications</td>
<td>Positive (n=579)</td>
</tr>
<tr>
<td>No</td>
<td>328 (70.7%)</td>
</tr>
<tr>
<td>Yes</td>
<td>82 (71.3%)</td>
</tr>
<tr>
<td>$X^2=0.017, p=.897$</td>
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Table 2 for sample females exhibits a radical shift in the data pattern. The “No” row again shows a prevalence percentage in the mid-twenties, but that figure nearly doubles in the “Yes” row. 46.2% of women who had one or more OCs have a negative diagnosis. The direct chi-square test of this difference is indeed statistically significant ($X^2=7.347, p=.007$), and strongly suggests an elevated risk for females only.

<table>
<thead>
<tr>
<th>Type of Schizophrenia by Obstetrical Complications for Females</th>
<th>Type of Schizophrenia</th>
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</thead>
<tbody>
<tr>
<td>Obstetrical Complications</td>
<td>Positive (n=207)</td>
</tr>
<tr>
<td>No</td>
<td>127 (75.6%)</td>
</tr>
<tr>
<td>Yes</td>
<td>21 (53.8%)</td>
</tr>
<tr>
<td>$X^2=7.347, p=.007$</td>
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**Analysis of Variance**

A somewhat more sophisticated appraisal of the hypothesis is permitted by the analysis of variance test displayed in Figure 1. The Y-axis represents the risk of negative (top) vs. positive (bottom) subtype calculated as a simple probability. The height of a given dot represents the mean risk for a
given category of patient; the higher the dot, the higher the risk of negative diagnosis. On the X-axis are three categories for the independent variable: “None” indicates no history of OCs, “One” indicates a single complication, and “Two Plus” indicates more than one OC. With a dichotomous dependent variable (0=positive, 1=negative) and, in effect, categorical independent variables, this is an appropriate subject for ANOVA.

Note that the male line is virtually flat, which means that the dots representing risk of negative subtype change little from category to category of the independent variable. Not so for the female line. The lowest risk by far is above the “None” category, then it rises significantly to the right. The risk of negative subtype soars above the “One” OC category, then changes little in the highest “Two Plus” category. The substantive interpretation is that any OC exposure elevated female risk of negative diagnosis, but multiple exposures makes no further difference; and, visually, there is no such effect for male patients. To bolster the visual with the statistical, the ANOVA test of the “Sex-OC effect” is statistically significant (F=3.025, p=.049). As suggested by the crosstabular analysis and as directly tested here, there is a sex-specified effect such that OCs elevate the risk of negative schizophrenia for females, but not for males.

Discussion

It has been established that OCs are associated with brain damage. This, in turn, has a role in the pathogenesis of some cases of schizophrenia (9). There is also literature linking brain abnormality with negative symptoms, a presentation of schizophrenia with poor prognosis (18, 19). The central finding of the present study further pinpoints the connection between OCs and negative symptomatology. Specifically, we find that the connection is present for females and not for males. What is the underlying basis for this gender-specific phenomenon? We offer two hypothetical explanations: first, our finding may connect with studies reporting that the male fetus is more fragile than the female fetus. Consequently, an OC may be more likely to prevent birth among males in the first place, whereas a similar insult to a female fetus may not result in spontaneous abortion but rather life with a brain abnormality. Simply stated, the males are more likely to die and the females are more likely to end up being psychotic.

There is a lot of evidence to support the “relative fragility” explanation. Male fetuses are more likely to result in premature rupture of the embryonic sac and suffer from un-
timely and difficult deliveries (47). Pregnancies of male fetsus are also associated with higher rates of labor dystocia, cord problems, fetal distress and significantly higher rates of non-reassuring fetal heart rate problems, all of which increase the likelihood of perinatal mortality (48). The list of elevated risk factors connected with male fetuses is lengthy and beyond the scope of this article. However, virtually all studies of the relative fragility of the male fetus report that male sex is an independent risk factor for adverse pregnancy outcome (49-52). Most germane to the present study is the established fact that the male fetus is at greater risk of death from almost all OCs that can occur before or during birth (53).

The second hypothetical explanation for our gender-specific finding of the connection between OCs and negative symptomatology is not inconsistent with the fact that the male fetus is more fragile. In fact, it is an independent interpretation. We hypothesize that there may be separate etiologies of negative symptoms for male and female schizophrenics. One causal route may be genetic and the other may be obstetrical. As suggested in this study, the causal route for females is an insult to the fetal brain inflicted by OCs. Other researchers suggest that negative symptoms in men stem from a greater biological vulnerability caused by stronger genetic penetrance (54).

Clearly, there is much more research needed to untangle the complex interplay of gender, genetics, and OCs in the genesis of schizophrenia with negative symptoms. As mentioned earlier, social class of origin may play an etiological role. Our recent research established a connection between OCs, negative symptoms and lower social class of origin (21). Additionally, our earlier research uncovered a curiously reduced risk for negative symptoms among males born into nonpoor families (55). We could not use SES as a covariate in this study because cell sizes became too small. The real explanations for the relationships above demand more variables in this study because cell sizes became too small. The second hypothetical explanation for our gender-specific effect in schizophrenia is determined through multiple forms of assessment that examine changing symptomatology over time. However, the data set employed in this study has limitations. It only includes patients from a single state mental hospital in the northeastern United States. Additionally, it does not include information about maternal infection during early trimesters, a potentially relevant variable. Consequently, the study findings must be considered as exploratory rather than definitive.

References


