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Obstetric complications and risk for conversion to psychosis among individuals at high clinical risk

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Abstract

Aim—Examining risk factors among high-risk populations stands to inform treatment and to elucidate our understanding of the pathophysiology of schizophrenia. Despite substantial evidence implicating the incidence of obstetric complications (OCs) as a risk factor for schizophrenia, little is known about the relationship between OCs and risk for conversion among high-risk individuals.

Methods—We prospectively followed individuals at high-risk for developing psychotic disorders for a 2-year period to determine if a history of OCs is associated with conversion.

Results—Individuals who converted to psychosis had significantly more OCs when compared to non-converting participants; a history of OCs was associated with increased odds of conversion (OR=4.90, CI:1.04/22.20). OCs were positively associated with prodromal symptomatology.

Conclusions—To date, this report represents the first empirical evidence suggesting that OCs confer increased risk of conversion to psychosis. It is possible that OCs interact with brain maturational processes in the pathophysiology of schizophrenia and can serve as a risk marker.

Keywords

Obstetric Complications; Prodromal; Conversion; Schizophrenia; Psychosis

Obstetric complications (OCs) are an integral component of a neural diathesis-stress model of schizophrenia, which posits that early brain lesions interacting with later neuroendocrine, neurodevelopmental and psychosocial factors result in the eventual presentation of clinical signs and symptoms of psychosis^{1,2}. In support of this theory, several studies have observed that a history of OCs is associated with earlier onset and a poorer course of illness^{3,4}. Although these investigations have provided evidence for OCs as a general putative marker, to date there has been little research aimed at determining if OCs confer a greater risk for

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conversion to psychotic disorders among clinical high-risk populations. Such ultra-high-risk (UHR) individuals exhibit a cluster of subthreshold psychotic symptoms, consistent with a prodromal syndrome, and have a roughly 35% rate of conversion to psychotic disorder over 2 years⁵.

If OCs are associated with conversion among UHR populations, this pattern would suggest a link between early neurodevelopmental insults and subsequent neuromaturational events thought to be related to the developmental pathogenesis of psychotic disorders during adolescence/early adulthood. Recent research suggests that early pharmacological and psychosocial interventions with UHR individuals can potentially improve the course of illness, or even prevent onset of psychosis⁶. Therefore, it has become priority to identify risk-markers that define those UHR individuals who are at the highest risk.

In the present study, high-risk individuals were assessed for a history of OCs and their diagnostic status was followed for a period of two-years. We hypothesized that a history of OCs would be associated with greater severity of symptomatology and a greater risk for conversion.

Method

Presentations describing the prodromal syndrome for psychosis were administered at local schools, hospitals, and community health care clinics and in addition, advertisements were placed on schizophrenia.com describing prodromal symptomatology in layperson terminology. Participants were evaluated through the Center for Assessment and Prevention of Prodromal States (CAPPS), a program at the University of California Los Angeles designed to identify and track individuals at genetic or behavioral risk for psychosis through the adolescent risk period (please see Meyer and colleagues (2005)⁷ for a detailed description recruitment and assessment procedures).

Participants underwent a screening assessment to determine the presence of a UHR syndrome (as assessed by the Structured Interview for Prodromal Syndromes; SIPS⁸); The SIPS⁸ defines a UHR syndrome by the recent onset of moderate to severe positive symptoms, and or a decline in global functioning accompanying the presence of schizotypal personality disorder. All individuals who met criteria were invited to participate in a longitudinal study. Assent and written consent were obtained from all participants and a guardian, in accordance with the guidelines of the university Human Subjects Review Committee and Institutional Review Board. Exclusion criteria included the diagnosis of Axis I schizophrenia-spectrum disorders, the presence of a neurological disorder, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnosis of drug or alcohol abuse or dependence, and/or an intelligence quotient below 70.

To assess for the presence of Axis I disorders, the Structured Clinical Interview for Axis I DSM-IV Disorders (SCID)⁹ or the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS)¹⁰ (for ages 14 and under) was administered during the Baseline, 6, months, 12-months, 2-year evaluations. Research has indicated that individuals identified as UHR using current criteria are at increased risk for developing schizophrenia as well as

affective disorders with psychotic features⁶. These findings are consistent with genetic evidence of shared etiological factors among DSM psychotic disorders^{11,12}. Consistent with this notion, the present study examines DSM Axis I psychosis, including both schizophrenia and affective disorder with psychotic features.

The occurrence of OCs was assessed during a parent interview, using the Lewis-Murray Obstetric Complications Scale¹³; the 15 item retrospective inventory encompasses a broad range of complications including events during the antepartum period (e.g., rubella, rhesus incompatibility, pre-eclampsia), the intrapartum period (e.g., premature rupture of membranes, long/difficult labor, cord prolapsed, cesarean, breech or abnormal presentation, forceps/vacuum delivery), and postpartum (e.g. low birthweight, incubator/resuscitation, gross physical anomaly; it has been widely used and has shown good reliability and validity¹³. The total number of endorsed items was computed for each participant. Diagnostic and OC interviews were conducted by advanced psychology doctoral students (MA level) or licensed clinical psychologists; Intraclass Correlations (ICCs) = 0.75 for all symptom ratings, $k = 0.80$ for prodromal syndrome and DSM-IV diagnoses were met by each interviewer. Diagnostic examiners were kept blind to OC status and the purpose of the study throughout data collection.

Results

Forty-seven UHR individuals ranging in age from 12 to 35 years participated in the present study. Of these participants, 9 converted to an Axis I psychotic disorder (19.15%) over the two-year follow-up. Pearson Chi-Square tests revealed no significant differences between *Converted* and *Non-Converted* groups in sex ratio [$\chi^2(1)=.93, p=.33$] or ethnicity [$\chi^2(4)=7.13, p=.13$], and a t-test indicated no group differences in age [$t(45)=.30, p=.76$]. Further, a series of t-tests indicated that there were no significant group differences in baseline positive [$t(45)=.05, p=.95, (Converted: mean=2.53, SD=1.02; Non-Converted: mean=2.51, SD=.90)$], negative [$t(45)=-.55, p=.58, (Converted: mean=2.42, SD=1.21; Non-Converted mean=2.20, SD=1.02)$], and total [$t(45)=-.55, p=.58, (Converted: mean=2.32, SD=.89, Non-Converted: mean=2.15, SD=.70)$] prodromal symptomatology. Thus, there were no significant between group differences in demographic or symptom variables at baseline. Table 1 provides a description of demographic characteristics and OC history for the sample and both groups.

An independent samples t-test showed significant differences in mean OC score between the *Non-Converted* (mean=1.60, SD=1.36) and the *Converted* group (mean=3.33, SD=2.73), indicating that UHR participants who converted to an Axis I psychotic disorder had a significantly more frequent number of OCs than those who did not convert [$t(45)=-2.75, p=.01, \eta^2=.14$].

Odds ratios were computed to determine the extent to which a history of OCs contributed to increased risk for conversion. Among the *Converted* group, 6/9 patients experienced at least one definite OC whereas among the *Non-Converted* group, 11/38 patients experienced a similar event. The analysis indicated that among prodromal participants, a history of at least

one definite OCs is associated with an approximately 5 times greater likelihood of conversion (OR=4.90, CI:1.04/22.20).

Bivariate correlations were conducted to determine the relationship between number of OCs and baseline prepsychotic symptoms, as assessed by the SIPS⁸. There was a moderate positive relationship between OCs and total symptoms ($r=.31$, $p=.01$) and a trend for a relationship between OCs and SIPS negative symptoms ($r=.22$, $p=.06$).

Discussion

Our finding that OCs are associated with conversion to psychosis among a UHR population suggests a link between early neurodevelopmental insults and later neuromaturational processes thought to be related to the developmental pathogenesis of psychotic disorders during adolescence/early adulthood. One possibility is that OCs resulting in fetal hypoxia may render the brain more vulnerable to later (post-pubertal) neurodevelopmental events, thus increasing the likelihood of conversion to psychosis³. This notion is consistent with evidence suggesting that temporal lobe regions vulnerable to hypoxia are also frequently implicated in the pathophysiology of schizophrenia,^{14,15}. Furthermore, since fetal hypoxia also results in a reduction of cell density in the hippocampus, a region responsible for regulating the hypothalamic-pituitary-adrenal axis¹, OCs may be indirectly responsible for the aberrant endocrine activity/stress-response characteristic of individuals with schizophrenia^{1,2,16}.

Yun and colleagues¹⁷ examined the incidence of OCs among a high-risk sample ($n=74$) and reported that OCs did not appear to be a significant risk factor. However, the authors noted several limitations in the study may have contributed to null findings and that it was premature to dismiss OCs as a risk factor¹⁷. In support of this conclusion, Ballon et al.¹⁸ recently examined 52 clinical high-risk individuals, and compared the incidence of OCs with non-psychiatric and schizophrenia comparison groups; the authors found comparable and significant elevations in OCs in the clinical ultra high-risk and schizophrenia groups. The trend of present findings may differ from the noted study conducted by Yun and colleagues¹⁷ because the period of investigation was extended (from 12 months to 24 months), and the criteria for conversion were more stringent (the definition of conversion was changed from an acute psychotic episode¹⁷ to formal DSM-IV criteria for an Axis I psychotic disorder).

It is important to note that OCs of the type coded for in this study occur in 15-20% of the general population, the majority of individuals who experience OCs do not develop psychosis, and a majority of individuals with schizophrenia have not had a detectable OC¹⁹. Thus, the present findings may apply to a minority of the population with psychotic disorders. A significant limitation is the reliance on parental report of OCs, as several studies have found that mothers of both schizophrenia and high-risk children show a tendency to over-report OCs²⁰. However, it should be noted that the information on OC history was collected before the parents or investigators knew whether any individual would develop psychosis. Another limitation relates to potential sampling bias; the recruitment strategy focused upon help-seeking individuals and therefore may not be representative of the general at-risk population.

Respectively, prodromal research is in a relatively nascent state. While the samples are currently small, important conclusions may be drawn from this growing body of research, particularly as prospective longitudinal designs offer a new perspective²¹. For example, prodromal studies with comparative samples size have been important in elucidating our understanding of other potential biomarkers associated with risk for conversion such a prenatal exposure to virus²² and hyperkinetic movements²³. Nonetheless, this present data should be interpreted as a pioneer study. Results from the present study suggest OCs as a useful candidate marker for identifying individuals who may stand to benefit most from preventive intervention; it is our hope that these preliminary findings will encourage and influence future research in this area.

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Table 1
Demographic Characteristics and Obstetrical History of High-Risk Sample

	Non-Converted Prodromal Group(n = 38)	Converted to Psychotic Disorder Group(n = 9)	Total Sample(n = 47)
<u>Age (yrs.)</u>			
M	16.39	16.06	6.32
(SD)	(3.05)	(2.15)	(2.88)
<u>Gender (%)</u>			
Males	60.5	77.8	63.8
Females	39.5	22.2	36.2
<u>Ethnicity (%)</u>			
African American	7.9	22.2	10.6
Caucasian	65.7	33.4	59.6
Asian American	-	11.1	2.1
Hispanic	13.2	22.2	14.9
Other	13.2	11.1	12.8
<u>Obstetric complications(%)</u>			
Rubella/Syphilis/HIV	-	11.1	2.1
Rhesus Incompatibility	2.6	-	2.1
Preeclampsia	2.6	-	2.1
Twin Birth Complicated	-	11.1	2.1
Cord Prolapsed	-	11.1	2.1
Premature Gestational Age	-	11.1	2.1
Cesarean	13.2	33.3	17.0
Breech Presentation	2.6	11.1	4.3
High/Difficult Forceps	5.3	-	4.3
Low Birthweight	-	22.2	4.3
Incubator/Resuscitation	2.6	33.3	8.5
Gross Physical Anomaly	2.6	-	2.1

Note: Percentages of OCs are based on items endorsed definite on the Lewis-Murray Obstetric Complications Scale; Items not endorsed by either group (antepartum hemorrhage, premature rupture of membranes, long/difficult labor) are omitted from the table.