Early Intervention IN PSYCHIATRY

Early Intervention in Psychiatry 2009; **3:** 226–230 doi:10.1111/j.1751-7893.2009.00137.x

Brief Report

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

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Received 9 October 2008; accepted 27 May 2009

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 two-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 (odds ratio = 4.90, confidence interval :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.

Key words: conversion, obstetric complications, prodromal, psychosis, schizophrenia.

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 conversion to psychotic disorders among clinical high-risk populations. Such ultra-high-risk (UHR) individuals exhibit a cluster of sub-threshold psychotic symptoms, consistent with a prodromal syndrome, and have a roughly 35% rate of conversion to psychotic disorder over two years.[5]

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 the onset of psychosis.[6] 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 a 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, a programme at the University of California Los Angeles designed to identify and track individuals at genetic or behavioural risk for psychosis through the adolescent risk period (please see Meyer and colleagues[7] for a detailed description of the 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 (SIPS)[8]). The SIPS[8] 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 the criteria were invited to participate in a longitudinal study. Assent and written consents 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[9] or the Kiddie Schedule for Affective Disorders and Schizophrenia[10] (for ages 14 and under) was administered during the baseline, 6-month, 12-month and 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 features.[6] These findings are consistent with genetic evidence of shared etiological factors among DSM psychotic disorders.[11,12] Consistent with this notion, the present study examined 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 Scale;[13] the15-item retrospective inventory encompasses a broad range of complications including events during the antepartum period (e.g. rubella, rhesus incompatibility, pre-eclampsia), the intra-partum period (e.g. premature rupture of membranes, long/difficult labour, cord prolapsed, Caesarean section, breech or abnormal presentation, forceps/vacuum delivery) and post-partum period (e.g. low birthweight, incubator/resuscitation, gross physical anomaly); it has been widely used and has shown good reliability and validity.[13] 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, $\kappa \geq 0.80$ for prodromal syndrome and DSM-IV diagnoses were met by each interviewer. Diagnostic examiners were kept blind to the OC status of the participants and the purpose of the study throughout data collection.

RESULTS

Forty-seven UHR individuals ranging from 12 to 35 years in age participated in the present study. Of these participants, nine converted to Axis I psychotic disorder (19.15%) over the two-year follow-up. Pearson's chi-square tests revealed no significant differences between the converted and non-converted groups in sex ratio ($\chi^2(1) = 0.93$, $P = 0.33$) or ethnicity ($\chi^2(4) = 7.13$, $P = 0.13$), and a *t*-test indicated no group differences in age ($t(45) = 0.30$, $P = 0.76$). Further, a series of *t*-tests indicated that there were no significant group differences in baseline positive ($t(45) = 0.05$, $P = 0.95$ (converted mean = 2.53, SD (standard deviation) = 1.02; non-converted mean = 2.51, SD = 0.90)), negative ($t(45) = –0.55$, $P = 0.58$ (converted mean = 2.42, SD = 1.21; non-converted mean = 2.20, SD = 1.02)) and total ($t(45) = –0.55$, $P = 0.58$ (converted mean = 2.32, SD = 0.89; non-converted mean = 2.15, SD = 0.70)) prodromal symptomatology. Thus, there was no significance 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 for both groups.

An independent sample *t*-test showed significant differences in mean OC scores between the non-

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)
Age (years)			
M (SD)	16.39 (3.05)	16.06 (2.15)	6.32 (2.88)
Gender (%)			
Male	60.5	77.8	63.8
Female	39.5	22.2	36.2
Ethnicity (%)			
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
Obstetric complications(%)			
Rubella/syphilis/HIV	–	11.1	2.1
Rhesus incompatibility	2.6	–	2.1
Pre-eclampsia	2.6	–	2.1
Twin birth complication	–	11.1	2.1
Prolapsed cord	–	11.1	2.1
Premature gestational age	–	11.1	2.1
Caesarean	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 obstetric complications are based on items endorsed as definite on the Lewis–Murray Obstetric Complications Scale; items not endorsed by either group (antepartum hemorrhage, premature rupture of membranes, long/difficult labour) are omitted from the table.
M, mean; SD, standard deviation.

converted (mean = 1.60, SD = 1.36) and converted groups (mean = 3.33, SD = 2.73), indicating that the UHR participants who converted to Axis I psychotic disorder had a significantly more frequent number of OCs than those who did not convert ($t(45) = -2.75$, $P \leq 0.01$, $\eta^2 = 0.14$).

ORs were computed to determine the extent to which a history of OCs contributed to increased risk for conversion. Among the converted group, 6 out of 9 patients experienced at least one definite OC, whereas among the non-converted group, 11 out of 38 patients experienced a similar event. The analysis indicated that among prodromal participants, a history of at least one definite OC is associated with approximately five times greater likelihood of conversion (odd ratio = 4.90, confidence interval: 1.04/22.20).

Bivariate correlations were conducted to determine the relationship between number of OCs and baseline pre-psychotic symptoms, as assessed by the SIPS.[8] There was a moderate positive relationship between OCs and total symptoms ($r = 0.31$, $P \leq 0.01$) and a trend for a relationship between OCs and SIPS negative symptoms ($r = 0.22$, $P = 0.06$).

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 psychosis.[3] 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 axis,[1] OCs may be indirectly responsible for the aberrant endocrine activity/stress-response characteristic of individuals with schizophrenia.[1,2,16]

Yun and colleagues[17] 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 factor.[17] In support of this conclusion, Balloon *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 the present findings may differ from the noted study conducted by Yun and colleagues[17] 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 episode[17] 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 OC.[19] 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 OCs.[20] 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. Although the samples are currently small, important conclusions may be drawn from this growing body of research, particularly as prospective longitudinal designs offer a new perspective.[21] For example, prodromal studies with comparative sample sizes have been important in elucidating our understanding of other potential biomarkers associated with risk for conversion such as prenatal exposure to virus[22] and hyperkinetic movements.[23] 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.

ACKNOWLEDGEMENTS

VAM's time was supported by Grant MH14584-33. This work was also supported by Grant MH52857 from the National Institute of Mental Health (to TDC). Additional support was provided by the Center for Computational Biology Grant U54 RR021813 and P41 Resource Grant RR013642 from the National Center for Research Resources. Funding was also provided by a gift to the UCLA Foundation from the Staglin Music Festival for Mental Health.

Author Mittal conducted statistical analyses and the literature search and wrote the first draft of the present manuscript. Author Willhite aided in the writing of the manuscript and in developing the theoretical conceptualizations. Author Niendam aided in the revision of the manuscript and in data collection. Author Bearden helped design the study, write the protocol, co-direct data collection and edit the manuscript. Author Daley provided psychiatric consultation throughout the study, co-directed data collection and edited the manuscript. Author Ellman aided in editing as well as providing conceptualization and theory used to integrate findings. Finally, Author Cannon helped design the study, write the protocol, obtain primary grant funding, direct data collection and edit the manuscript. All authors contributed to and have approved the final manuscript.

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