At Issue: The Problem of Obstetrical Complications and Schizophrenia

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Abstract

The use of the term "obstetrical complications" (OCs) and its variations to encompass diverse physiological mechanisms (e.g., genetic, ischemic, hemorrhagic, infectious) of disruption to fetal/neonatal brain development has engendered inconsistency, confusion, and controversy. The principal reason is that the term OCs belies the absence of a fully adequate conceptual framework for characterizing neurodevelopmental risk. We propose that neurodevelopmental risk factors for schizophrenia can be assessed more clearly if broad OC scales are replaced by measures representing more homogeneous pathways of disturbed brain development. Using a new OC classification, we found that disordered growth related to hypoxic-ischemic compromise to early brain development may confer an elevated risk of schizophrenia and other adult-onset psychoses, particularly in the presence of familial risk. Abnormal fetal and neonatal brain growth and development in schizophrenia and OCs may also, at least in part, result from genetic factors and could help explain the relation between seemingly inconsistent OCs identified in prior research.

Keywords: Schizophrenia, obstetrical complications, epidemiology.


Difficult birth in itself in certain cases is merely a symptom of deeper effects that influence the development of the fetus or the organism of the mother.

—Sigmund Freud (1897, p. 208)

Although of growing relevance to the etiology of schizophrenia, obstetrical complications (OCs) have continued to pose daunting challenges to definition and measurement. One of the principal reasons for stalled progress in the field has been the absence of a unified conceptual framework guiding the definition (Zornberg 1997) despite the thorough enumeration of hypothetical extrinsic and genetic pathways of risk (and their potential interactions) relating OCs to schizophrenia (McNeil and Kaij 1978).

The endeavor to clarify the nature of the relation between OCs and schizophrenia entails the successive refinement of indices of disturbed brain development that are valid, reliable, and responsive to changes fueled by the rapid pace of progress in the neurosciences. Yet the selecting, weighting, and summarizing of OC factors have varied greatly among studies (McNeil et al. 1994; McNeil 1995). In the absence of agreed-upon criteria based on biological mechanisms, there is little basis for the comparison of findings among studies.

OC Scales and Their Limits. As the demand for standardized measures of risk first arose in schizophrenia research, very few OC scales were available. Not infrequently, existing instruments were created from other scales (Lewis and Murray 1987). OC scales have generally been designed to measure indices of obstetrical health, broadly defined as conditions during the mother's pregnancy combined with factors related to the delivery and neonatal health status scales (Parnas et al. 1982; Lewis and Murray 1987). The
scales that have been developed have differed in method of construction, in intended source of information (mother or birth records), and in reliability and validity (McNeil et al. 1994; McNeil et al. 1997). The two most common features underlying the application of general OC scales are the implicit assumptions of a unitary effect and a dose-response effect on the risk of schizophrenia. Both assumptions can be challenged.

The use of summary scores from OC scales reflects the notion of a unitary class of risk for schizophrenia (McNeil 1995). With wide-ranging arrays of prenatal and neonatal factors combined under one OC rubric, irrespective of pathway of risk (e.g., infection, hemorrhage, necrosis) (Gilles 1985), there is a supposition that the grouped factors act similarly on brain development. Whether the varied factors combined into a summary score have the same effect on brain formation remains—at best—equivocal. For instance, neonatal hemorrhagic events may pose different anatomical and long-term consequences for brain development than prenatal viral infection does (Freeman 1985; Gilles 1985). Out of necessity, some investigators had resigned themselves to the use of “atheoretical” (Lewis and Murray 1987) or broad-definition OC scales (Parnas et al. 1982) as the means to detect reliably at least a significant association with schizophrenia. At that point, the evidence regarding OCs (based largely on maternal recall or unsystematic birth records) was inconclusive. Nonetheless, while these methods of several decades past were instrumental in advancing general knowledge of the relation between OCs and schizophrenia, they now require modification for the current generation of neurodevelopmentally guided epidemiologic investigations.

The dose-response assumption implies that the greater severity or number of OC factors corresponds to more severe injury or greater likelihood of schizophrenia, in keeping with the well-known theory of “a continuum of reproductive casualty” (Pasamanick et al. 1956, p. 613). Nonetheless, despite its intrinsic appeal, experts in fetal medicine have found little cogent evidence to support the “continuum of reproductive casualty” to brain development as measured by standard OC scales:

Rather, there appear to be thresholds beyond which damage becomes manifest. For example, there appear to be degrees and/or durations of hypoxia tolerated without obvious effects on mental or motor function, yet, when the duration or severity of hypoxia exceeds these thresholds, motor dysfunction results and may be accompanied by severe retardation or epilepsy. (Freeman 1983, p. 14)

In addition to neglecting to acknowledge the influence of constitutional thresholds of extrinsic risk to brain formation and maturation, the dose-response model fails to acknowledge subtle, deviated brain processes that are the substrate for schizophrenia and that remain undetectable to extra-uterine observation (Goldman-Rakic 1995).

Obstetrical Complications or Abnormalities of Fetal and Neonatal Brain Development? Considering the subtlety of many of the putative brain abnormalities found in postmortem research (Benes and Bird 1987; Jakob and Beckmann 1989), it is remarkable that such indirect markers as adverse maternal health conditions during gestation would show an association 20 years later with schizophrenia. Even fetal and neonatal brain lesions that are severe may be easily missed at the time of the event. For example, 50 percent of preterm infants with periventricular-intraventricular hemorrhage detected by noninvasive cranial imaging techniques do not show clinical signs of hemorrhage (Papile 1992). This uncertainty generated by the inconsistency engenders doubt as to whether conditions predisposing to schizophrenia have been taken into account (McNeil et al. 1997). One problem with measuring abnormal pregnancy conditions jointly with neonatal conditions is that they may reveal more about the mother’s health than her infant’s brain development.

Despite the headway that has been made over four decades of vigorous research, the exact nature of OCs most relevant to the pathophysiology of schizophrenia remains unknown.

To assess the existence and magnitude of each influence on the developing brain, it is critical to benchmark indicators of disturbed fetal and neonatal brain involvement associated with more homogeneous pathways of risk (Zornberg 1997). The final outcome will depend on the physiological pathway, severity, anatomical location, and timing of the disturbance during brain development—all within the context of constitutional resiliency such as cerebral plasticity, perfusion, immune response, and cerebrovascular integrity (Freeman 1985; Benes 1995; McNeil 1995).

Consequently, the relatively recent introduction of the McNeil-Sjöström OC scale (1994) has advanced the field of measurement by allowing comprehensive, systematic data to be collected with respect to timing, severity, and physiological mechanism of the OCs. Moreover, in keeping with the notion of heterogeneity in the etiology of schizophrenia (Tsuang and Faraone 1995), pathways of early risk that have been explored include malnutrition (Susser et al. 1996), hypoxia (Buka et al. 1993; Jones et al. 1998; Dulman et al. 1999), Rh incompatibility (Hollister et al. 1996), and viral infection (Mednick et al. 1988; O’Callaghan et al. 1991; Kunugi et al. 1992).

New Directions in the Classification of OCs. Introducing a novel strategy in a followup study of 693 individuals in Providence, Rhode Island, Zornberg et al. (2000) reported
an elevated, graded risk of schizophrenia and other nonaffective psychoses associated with a classification of OCs derived to be related to genetic disorders of growth and development (Gill 1994) and also to vulnerability to hypoxic-ischemic brain injury in the neonate (Amiel-Tyson 1995), but not necessarily indicative of actual hypoxic brain damage. The method driving this strategy of OC classification centered on linking early occurring factors such as preeclampsia (McNeil and Kaja 1978; Dalman et al. 1999) and uterine bleeding (Sacker et al. 1995; Waddington et al. 1998) to disordered neonatal growth and development manifested in dysmaturity or postterm birth (Parnas et al. 1982; Gillberg et al. 1986) and intrauterine growth retardation (Hultman et al. 1994). On further analysis, a stronger (though statistically nonsignificant) risk of psychosis was found related to this hypoxia-ischemia–related classification of OCs in those individuals with familial risk of psychosis or mood disorders compared with those reporting no familial risk (Zomberg 1997; Zomberg et al. 2000), while prenatal maternal viral infections were more common in the absence of familial risk (Zomberg 1997). These data are consistent with findings from other studies of a positive association between certain classes of OCs and familial risk (Parnas et al. 1982; Cannon et al. 1997; Kinney et al. 1998), providing additional evidence in support of the concept that genetic factors involved in schizophrenia may confer an enhanced vulnerability to hypoxic-ischemic brain injury.

This new strategy linking markers of abnormal neonatal growth and development to earlier disturbances during fetal brain development shifts the OC measure from a set of grouped factors (in which one factor is sufficient to classify the individual as positive for the OC category) (Parnas et al. 1982) to specific patterns of prenatal and neonatal abnormalities associated with an underlying pathway of risk of disordered reproduction, growth, and development related to hypoxia-ischemia (Zomberg et al. 2000). The impetus for the focus on OCs associated with this hypoxia-ischemia–related pathway of risk to early brain growth and development drew in part from the resemblance between patterns of abnormalities in doro-lateral prefrontal regions of the cortex in studies of schizophrenia (Andreasen et al. 1994) and the distributions of brain lesions commonly found in full-term infants suffering more severe hypoxic-ischemic brain injury (involving the dorsal and peripheral cortical, subcortical gray matter) (Brann and Schwartz 1992).

Consequently, certain significant OCs that have seemed unrelated in schizophrenia research such as preeclampsia (McNeil and Kaja 1978; Dalman et al. 1999) and retarded fetal growth (Hultman et al. 1994; McGrath et al. 1999) can now be reexamined in the context of this new conceptual framework. Is it possible that underlying genetic influences that give rise to conditions such as severe preeclampsia and intrauterine growth retardation (Gill 1994)—and are associated with vulnerability to hypoxic-ischemic compromise to neonatal brain development (Amiel-Tyson 1995)—may contribute to the pathophysiology of schizophrenia?

Though not conclusive, several lines of evidence support a relation between abnormalities of reproduction, growth, and development and the risk of schizophrenia. On the one hand, reduced fertility (attributed to genetic factors) has long been noted in schizophrenia patients (Huxley et al. 1964; McGrath et al. 1999). On the other hand, not only are OCs found in the birth experience of those who succumb to schizophrenia, numerous disorders of reproduction have been noted in their mothers' other reproductions, including miscarriages, prematurity, and stillbirths (Kraepelin 1919). In women who were nulliparous prior to the index birth, mothers of offspring with schizophrenia manifest higher rates of complicated prenatal histories (including difficult labor and delivery) than mothers of comparison offspring (Jablensky et al. 1998). In longitudinal research, delays in neuromotor and cognitive development antecedent to schizophrenia have been attributed to genetic factors rather than OCs (Fish et al. 1992). Dysmorphic features and subtle disorders of neureonal migration during brain development, if not caused by drugs or infection, tend to be caused by the early factors of genetic or chromosomal disorders during the first half of pregnancy (Lyon 1995; Waddington et al. 1998).

Discussion

Clearly, the introduction of the concept of OCs into etiologic research has been influential in sparking heightened interest in alternative risk factors and preventive interventions for schizophrenia. However, the discrepancies between the numerous approaches to measuring OCs highlight the difficulties that continue to hinder the achievement of a shared paradigm of risk. Broad OC definitions should now be replaced systematically by more refined classifications of abnormal fetal and neonatal brain development related to homogeneous pathways of risk. These sets of particular OC factors derived from fetal and neonatal medicine associated with each physiological pathway may then be linked further to underlying etiologies.

Using a new OC classification of prospectively collected OC factors, the findings suggested that disordered growth related to hypoxia-ischemic compromise to early brain development may confer an elevated risk of schizophrenia and other adult-onset psychoses, particularly in the presence of familial risk. With respect to the possibility that genetic disorders of reproduction, growth, and development (Gill 1994) may be related to this new OC predictor of schizophrenia, significant OCs that have been
considered unrelated in prior research may prove to be related as manifestations of an underlying polygenic etiology of psychotic disorders. One approach that has not yet been employed in the identification of individuals at high risk is the examination of the effect of maternal-fetal genetic compatibility (Ober 1992) as predictive of both OCs and schizophrenia. However, before DNA-based analyses are undertaken (Kidd 1997), it is important to learn as much as possible about OCs and their relation to genetic factors from population and family studies.

References


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