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The Role of Obstetric Events in Schizophrenia

Mary Catherine Clarke[1,2], Michelle Harley[2], and Mary Cannon[2]

[2]Department of Psychiatry, Royal College of Surgeons in Ireland, Dublin, Ireland

What We Already Know

It is now well established that obstetric complications or obstetric events increase the risk for schizophrenia. This is a small effect—the pooled odds ratio of the effect of exposure to obstetric complications on the subsequent development of schizophrenia has been estimated to be about 2.0 (95% confidence interval, 1.6–2.4).[1–3] The term ''obstetric complications'' covers a wide range of events, and for many years researchers have tried to tease apart this association in order to identify the one complication or underlying mechanism that is responsible for the increase in risk. Results from large population-based studies have been pooled to give substantial sample sizes for meta-analysis. Yet no one unifying mechanism has emerged. The most parsimonious approach at present may be to group complications of apparently similar modes of action together. The three ''groups'' that have emerged from the literature to date are (a) fetal growth retardation, (b) fetal perinatal hypoxia, and (c) prenatal complications.[1]

Fetal Growth Retardation

Lower birth weight among individuals who later develop schizophrenia than among controls has been one of the most consistent findings in the literature to date.[1] Smaller head circumference and being small for gestational age have also been associated with schizophrenia, pointing to an underlying mechanism of fetal growth retardation.[4,5] It has been postulated that this fetal growth retardation is mediated by genetic effects, as mothers with schizophrenia also have higher rates of low birth weight among offspring.[5–7] Nilsson et al.[8] examined this issue in same-sex twins discordant for schizophrenia and found that within these twin pairs, low birth weight and smaller head circumference were significantly associated with later development of schizophrenia, indicating that the fetal growth restriction may be independent of familial factors. However, as noted by Rapoport et al.,[9] almost any factor adversely affecting the fetus will affect its growth, so this association is not particularly informative from the point of view of pathogenesis. We could also conceptualize fetal growth retardation as one of the earliest manifestations of the neurodevelopmental trajectory of schizophrenia, which includes decrements in motor, language, and cognitive performance from infancy throughout childhood.[10,11]

Fetal/Perinatal Hypoxia

It has long been recognized that individuals with schizophrenia were more likely to have experienced a cluster of obstetric complications involving hypoxia than were controls.[1,4,12–16] Taking this association a step further, Cannon and colleagues in Finland and the United States have reported intriguing interaction effects between fetal hypoxia and genetic risk for schizophrenia on brain structure.[17] Using cases and controls drawn from population-based registers in Finland, the researchers have found that a history of fetal hypoxia is associated with greater structural brain abnormalities in probands with schizophrenia than among controls.[18,19] This leads to the hypothesis that reductions in gray-matter volume in certain cortical and subcortical regions, including the hippocampus, derive at least in part from the interacting influences of an inherited genotype for schizophrenia and hypoxic complications in utero. Interestingly, the effects of fetal hypoxia were two to three times greater among cases born small for gestational age,[18] further increasing the complexity of the issue and showing the possibility of an interaction between obstetric events as well as between genotype and obstetric events.

Prenatal Risk Complications

Not all obstetric complications get recorded on birth records, and there is an emerging literature on a wider range of prenatal risk factors, such as prenatal stress, intrauterine malnutrition, and prenatal infection, which use ecological sources of information.[20] The list of such prenatal risk factors associated with later schizophrenia

[1]To whom correspondence should be addressed; tel: +353 1 809 3854, fax: +353 1 809 3741, e-mail: maryclarke@rcsi.ie.

Table 1. Prenatal Risk Factors for Schizophrenia

Risk Factor	Author	Description
(1) Infections*		
(A) Influenza	Mednick et al. (1988)[21] Kendell and Kemp (1989)[22] O'Callaghan et al. (1991)[23] Torrey et al. (1992)[24] McGrath et al. (1994)[25] Erlenmeyer-Kimling et al. (1994)[26] Izumoto et al. (1999)[27]	Most studies that examined the effect of exposure to the 1957 influenza epidemic during pregnancy (2nd trimester) found a relatively increased risk (1.5–2.0) of later developing schizophrenia.
(B) Other infections	Brown et al. (2000a)[28]	2nd-trimester exposure to a wide variety of respiratory infections was associated with a significantly increased risk of schizophrenia spectrum disorders (adjusted relative risk 2.13).
	Brown et al. (2000b)[29]	1st-trimester exposure to rubella led to a substantially higher relative risk (5.2) of developing non-affective psychoses.
	Suvisaari et al. (1999)[30]	2nd-trimester exposure to poliovirus infection was found to increase the relative risk for the later development of schizophrenia (1.05: 0.99–1.10).
(C) Archived serum	Brown et al. (2004)[31]	Examination of archived maternal serum showed that the risk of schizophrenia increased sevenfold following influenza exposure during the 1st trimester of pregnancy.
	Brown et al. (2005)[32]	Maternal exposure to toxoplasmosis increased risk of schizophrenia/schizophrenia-spectrum disorders (OR 2.61:1.00–6.82).
	Buka et al. (2001)[33]	The offspring of mothers with elevated levels of antibodies to the herpes simplex virus type 2 were found to be at a significantly increased risk for the development of schizophrenia and other psychotic illnesses in adulthood (P = .02).
(2) Medication		
	Sorensen et al. (2004)[34]	Prenatal exposure to analgesics in the 2nd trimester was associated with an increased risk of schizophrenia (OR 4.75:1.9–12.0).
	Sorensen et al. (2003)[35]	Prenatal exposure to both hypertension and diuretic treatment in the 3rd trimester conferred a 4.01-fold (95% CI = 1.41–11.40) elevated risk.
(3) Nutritional Deficiency		
	St. Clair et al. (2005)[36]	Prenatal exposure to the Chinese famine of 1959–1961 significantly increased risk of schizophrenia in later life (adjusted relative risk: 2.30, 1.99–2.65, for those born in 1960, and 1.93, 1.68–2.23, for those born in 1961).
	Susser and Lin (1992)[37] Susser et al. (1996)[38] Hoek et al. (1996)[39]	Birth cohorts exposed to the 1944–1945 Dutch Hunger Winter in early gestation had a twofold increase in risk for schizophrenia
(4) Stress		
	Dalman et al. (2005)[40]	Paternal death during fetal life was associated with an increased risk of developing psychosis later in life (HR 2.4: 1.4–4.0). This replicates the classic finding of Huttunen and Niskanen (1978).
	Kinney et al. (1999)[42]	Prenatal exposure to a natural disaster (a severe tornado) during vulnerable weeks of gestation was associated with increased risk of schizophrenia.
	Van Os (1998)[43]	Increased relative risk of schizophrenia (1.28: 1.07–1.53) among those in the Netherlands who were in utero (1st trimester) during the Nazi invasion in May 1940.
	Myhrman et al. (1996)[44]	The risk of later schizophrenia among unwanted children was raised compared with wanted or mistimed children, even after adjustment for confounding by sociodemographic, pregnancy, and perinatal variables (OR 2.4:1.2–4.8).
(5) Rhesus Incompatibility		
	Hollister et al. (1996)[45]	The rate of schizophrenia was found to be significantly higher in an Rh-incompatible group (2.1%) compared with the Rh-compatible group (0.8%).

*See article by Brown, this series, for comprehensive overview of prenatal viral exposure.

continues to grow exponentially (see Table 1[21–45]). The one factor that unites these disparate risk factors is the size of the effect, as odds ratios of around 2.0 are almost invariably reported.

These prenatal risk factors do not yet seem to hang together under a cohesive pathogenic framework that unites prenatal infection, prenatal malnutrition, and maternal stressors of varying degrees of severity. A prenatal stress model with enhanced glucocorticoid secretion or release of inflammatory cytokines as the potential common mechanism mediating enhanced risk for schizophrenia has been invoked,[46] but there is as yet no definitive evidence for this. Animal studies may be utilized to test these theories.[47]

Gene-Environment Interactions and Prenatal Complications

As with fetal hypoxia, research into these prenatal factors is now moving from merely listing associations to examining possible interactions with genotype. This can be approached from a number of angles:

(*1*) *Prenatal complications increasing the risk of genetic mutations.* The association between increased paternal age and an increased risk of later schizophrenia was first described in the *British Journal of Psychiatry* by Hare and Moran.[48] This finding has been consistently replicated by others and is felt to be independent of personality or social factors.[49–53] It is proposed that de novo mutations, possibly X-linked, associated with increased paternal age may be responsible for this association.

(*2*) *Genotype increasing risk of adverse prenatal environment.* It has been reported that rhesus incompatibility increases risk for later schizophrenia, but it was not known how this mechanism operated.[1,45] A direct toxic effect of hyperbilirubinemia on the developing brain was proposed.[20,45] However, a family study from Finland has demonstrated that the RHD locus increases risk for schizophrenia through a maternal-fetal genotype incompatibility mechanism that increases risk of an adverse prenatal environment.[54] This is the first maternal-fetal genotype incompatibility effect described in schizophrenia.

(*3*) *Maternal genotype increasing risk of behaviors detrimental to fetal environment.* Obstetric complications, particularly low birth weight, stillbirths, and fetal or neonatal deaths, occur significantly more frequently among offspring of schizophrenic mothers compared with comparison groups.[5,7,55] The literature is remarkably consistent in this regard. Is the increased rate of obstetric complications in this group an effect of a maternal schizophrenia genotype, or is it secondary to a cluster of adverse environmental factors? The answer seems to be ''a bit of both.'' Jablensky et al.,[7] in a large Australian cohort study of women with schizophrenia, found that the clustering of adverse maternal characteristics among women with schizophrenia (such as low socioeconomic group, increased rates of smoking, lack of social support, and non-optimal maternal age) was a major contributing factor to the increased risk of obstetric complications in this group. However, when these maternal factors were controlled for, the incidence of adverse outcomes in women with schizophrenia remained significantly increased—although only in pregnancies occurring after illness onset. One must bear in mind the possibility of residual confounding by socioeconomic factors and adverse effects of antipsychotic medication during pregnancy, but a complex interaction between maternal genotype, maternal behavior, and prenatal environment is a likely explanation for this cluster of findings.

Embracing Complexity

It is time for us to regard obstetric complications in a new light. From an epidemiological perspective, it is evident that what we are dealing with are very small risk factors for a relatively rare disorder. Power issues will always be paramount and will continue to be responsible for seemingly contradictory results from studies of apparently similar design. An entirely clear picture may never emerge, but the lack of specificity may in itself be informative. Obstetric events are, by their nature, inextricably interlinked. Any complication during pregnancy is likely to increase the risk of further pregnancy complications and impact on the eventual labor and delivery. For instance, gestational diabetes is associated with increased risk for pre-eclampsia, and both increase the risk of delivery complications. In addition, the window of vulnerability appears to extend even beyond birth, since neonatal CNS infections also seem to increase risk for later schizophrenia.[56] Maternal characteristics and behavior significantly affect the well-being and development of the fetus and, in turn, pregnancy complications will affect the mother's psychological and physical well-being. Underlying all this we have the complex interrelationships between maternal and fetal genotypes and maternal and fetal environments. Animals exposed to obstetric insults have a ''sensitized'' dopaminergic transmission and are more susceptible to later environmental stressors.[57] We are gaining more information about later risk factors for schizophrenia (as outlined in other articles in this series), such as cannabis use, urbanisation, immigration, social adversity, and life events[58] that could contribute to such a causal model.[58–61]

A New Way to Conceptualize Obstetric Complications

Obstetric complications undoubtedly play a role in the etiology of schizophrenia, but the nature and strength of the association are unclear. They constitute a nonspecific risk factor of small effect and are implicated

in a range of other physical and psychological disorders.[62,63] It is evident that obstetric complications are neither necessary nor sufficient causal factors for schizophrenia. Obstetric complications occur in approximately 25–30% of the general population (depending on the definition),[1] and the vast majority of people with obstetric complications do not develop schizophrenia. Equally, a majority of individuals with schizophrenia have not had a detectable obstetric event. It is evident that obstetric complications are neither necessary nor sufficient causal factors for schizophrenia and may be most successfully described as component causes.[60,63,64] In other words, obstetric complications form a part of the causal pathway to schizophrenia (or a part of the causal "pie") for some individuals but not all. To paraphrase Kendler[65] in his discussion of genetic risk factors, the impact of individual (obstetric complications) on risk for schizophrenia is "*small, often non-specific and embedded in causal pathways of stunning complexity*." However, just as with genetic risk factors, one should not ignore a risk factor because it is of small effect. It is likely that obstetric events moderate the effects of genetic or other environmental risk factors for schizophrenia.[66] Obstetric complications remain one of the best-replicated "environmental" risk factors for schizophrenia and should stay at the forefront of our quest to elucidate the causal mechanisms and gene-environment interactions leading to this complex disorder.

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