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NATURE OF OBSTETRIC COMPLICATIONS IN SCHIZOPHRENIA

While Kendell *et al* (2000, this issue) are to be commended for reporting what appears to be an artefact that renders their previous study unreliable, their present analyses raise new challenges. These largely (but not entirely) negative findings have to be interpreted in the context of: (a) the three recent birth-cohort studies cited by Kendell *et al*, each of which reports risk for schizophrenia to be associated significantly with one or more obstetric complication(s); and (b) a recent meta-analysis of 12 previous case–control studies which indicates in schizophrenia an odds ratio of 1.38 (95% CI 1.05–1.84, $P=0.02$) for exposure to at least one 'definite' complication (Geddes *et al*, 1999).

At a general level, discrepancies between a meta-analysis and a subsequent large, controlled trial are a well-recognised phenomenon in medical research that attract considerable attention; the most parsimonious conclusion in such circumstances is that a discrepant controlled trial does not negate the meta-analytic findings but, rather, suggests heterogeneity between studies that prompts identification and incorporation of covariates which reduce such heterogeneity (DerSimonian & Levine, 1999). The same principle may be just as applicable to the conundrum of obstetric complications in schizophrenia, but what approach should be taken?

As noted elsewhere (Waddington *et al*, 1999*a*,*b*), schizophrenia researchers have concerned themselves overwhelmingly with which and how obstetric complications might impart damage to the nascent nervous system, in the manner of stochastic (random/probabilistic) events; conversely, obstetricians adopt a different perspective and vocabulary, concerning themselves equally with what is to them a fundamental issue of why vicissitudes of pregnancy and delivery occur, on the basis that they arise for a reason rather than stochastically. It is enigmatic why many schizophrenia researchers remain preoccupied with the concept of obstetric complications only as a source of direct cerebral insult to a previously normal foetus, when obstetricians themselves readily conceptualise such complications as arising in considerable part due to events acting earlier in pregnancy. Some of their epidemiological findings are of considerable relevance both to schizophrenia and to how the findings of Kendell *et al* might be accommodated.

Among the general population, complications of late pregnancy and delivery, the period implicated perhaps most consistently (although by no means exclusively) in relation to schizophrenia, are associated with events in early foetal life. For example, breech-birth and cord prolapse are each more common among babies having congenital anomalies, as are bleeding in early pregnancy, pre-eclampsia and premature delivery. Given the origin of congenital anomalies in dysmorphogenesis over embryonic and early foetal life, these findings relate such 'late' and other obstetric complications to, and at least in part 'root' them in, otherwise unspecified events which have already compromised the foetus over the first or early second trimester (see Waddington *et al*, 1999*a*,*b*).

On this basis, as patients with schizophrenia appear to show a characteristic topography of subtle, craniofacial and other dysmorphology (minor physical anomalies/dysmorphic features), arising most likely between weeks 9/10 and 14/15 of gestation, any excess of later obstetric complications therein could reflect an already compromised foetus (Waddington *et al*, 1999*a*,*b*); this would be in accordance with Kendell *et al* quoting that obstetric complications in schizophrenia "appeared to be due largely to characteristics of the child, not the delivery". There are few data on the relationship between physical anomalies and obstetric complications in schizophrenia, and these are not consistent (O'Callaghan *et al*, 1991; McNeil & Cantor-Graae, 1999). However, in focusing on the prior integrity of the conceptus, one might explain differences between studies in terms of developmentally determined severity/chronicity of patient illness in the face of as inherently high threshold/low sensitivity a measure as obstetric complications; it may be relevant that patients in the study of Kendell *et al* were aged between 18 and 26 years, and diagnosed using ICD–8/9 (World Health Organization, 1974, 1978), in whom severity/chronicity of illness would have been less clear, while the majority of patients in the meta-analysis of Geddes *et al* (1999) were of established chronicity and had been diagnosed according to DSM–III/III–R criteria (American Psychiatric Association, 1980, 1987). Furthermore, it is well recognised, even on meta-analysis (Geddes *et al*, 1999), that it is difficult to resolve any particular complication(s) as bearing a specific pathological relationship to schizophrenia; this might also be consistent with earlier events leading to diversity of sequelae along the complex time-line of human pregnancy. Such a line of reasoning might explain an apparently small population-attributable fraction for obstetric complications in schizophrenia (Geddes *et al*, 1999), and would predict further inconsistent findings among diverse patient populations; the 'true' picture is likely to become clear only on the continuing application of appropriate meta-analytic techniques, and by further study of what may be antecedent factors.

It should be emphasised that such a perspective in no way diminishes the adverse impact of 'late' complications on the nascent brain on an individual patient basis; rather, it focuses attention on earlier, primary events that contribute to the emergence thereof, and on their further adverse impact on an already compromised nervous system. The data of Kendell *et al* should be seen as an important stimulus for revising our perspectives on the nature of obstetric complications in schizophrenia.

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