Obstetric complications and schizophrenia: prenatal underdevelopment and subsequent neurodevelopmental impairment

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Background Many studies have shown an association between obstetric complications and schizophrenia.

Aims To investigate the possible relationship between prenatal underdevelopment, neurodevelopmental abnormality and subsequent schizophrenia.

Method The literature was reviewed. In particular, by pooling data from recently published reports, we examined whether low birthweight (<2500 g) is a risk factor for schizophrenia.

Results Low birthweight was significantly more common for subjects with schizophrenia than for control subjects: $P<0.00001$, odds ratio 2.6 (95% CI 2.0 to 3.3). Individuals born prematurely are at greater risk of perinatal brain damage and subsequent neurodevelopmental abnormalities, which may constitute vulnerability to the development of schizophrenia. Patients with schizophrenia who had low birthweights also tended to have poor premorbid psychosocial adjustment.

Conclusions Low birthweight is a modest, but definite, risk factor for schizophrenia. Brain damage associated with prenatal underdevelopment has a role in the pathogenesis of poor premorbid functioning and subsequent neurodevelopmental impairment in some cases of schizophrenia.

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AETIOLOGICAL ROLE OF OBSTETRIC COMPLICATIONS IN SCHIZOPHRENIA

Schizophrenia, particularly in its severe form, has been reformulated as a neurodevelopmental disorder (Murray, 1994). Several lines of evidence from epidemiological, neuroimaging and post-mortem studies have suggested that at least a portion of adult schizophrenia results from neurodevelopmental impairment early in life. A number of studies have shown possible risk-increasing effects of obstetric complications (OCs) on the development of schizophrenia.

The view that OCs could have a pathogenic effect dates back to the 1950s. Pasamanick *et al* (1956) examined OCs in children with behaviour disorders. They concluded, "there exists a relationship between certain abnormal conditions associated with childbearing and the subsequent development of behaviour disorder in the offspring". They proposed the hypothesis of a continuum of reproductive causality consisting of brain damage incurred during prenatal and paranatal periods, leading to a gradient of injury extending from foetal and neonatal death through cerebral palsy, epilepsy, mental deficiency and behaviour disorder.

Subsequent studies have examined OCs in childhood schizophrenia, adult schizophrenia and the offspring of parents with schizophrenia. McNeil & Kaij (1978) reviewed the literature and concluded that OCs are a risk-increasing factor to be taken seriously in the aetiology of adult schizophrenia. Thereafter, more than 20 case–control studies and some cohort studies have examined the association between OCs and adult schizophrenia. Although the diagnostic criteria and assessment of OCs varied from study to study, the majority showed an increased rate of OCs in schizophrenia compared with controls. Geddes & Lawrie (1995), who performed a meta-analysis combining 23 data-sets, found that subjects exposed to OCs were twice as likely to develop schizophrenia. Although most of the subjects included in this meta-analysis were from European populations, similar findings were obtained in a comparison of Japanese patients with schizophrenia and controls (Kunugi *et al*, 1996*a*).

However, the mechanisms underlying the relationship between OCs and schizophrenia are unclear. OCs include a variety of obstetric events, such as disease of the mother during pregnancy, abnormal foetal position, prolonged labour, foetal distress at delivery, low birthweight and diseases in early infancy. Although several OCs have been reported to be associated with schizophrenia (Table 1), no specific complication has been consistently found to be associated with schizophrenia. This may be attributable in part to the small sample sizes of the individual studies, and to the difficulty of obtaining obstetric data from a large number of subjects, especially when researchers attempted to obtain recorded obstetric data rather than retrospective information from interviews with mothers of patients with schizophrenia. In addition, it is possible that each single OC has only a weak effect on the development of schizophrenia.

In this context, obstetric records from a large number of subjects are required to clarify the link between OCs and schizophrenia. Furthermore, it is important to examine each individual complication meticulously in relation to any possible causal relationship with schizophrenia. Among the many items included under the term 'obstetric complications', we focus here on the role of intra-uterine growth.

INTRA-UTERINE PHYSICAL GROWTH AND BRAIN DEVELOPMENT IN SCHIZOPHRENIA

Birthweight

Mean birthweight has been reported to be lower among patients with schizophrenia than among controls (McNeil *et al*, 1993; Sacker *et al*, 1995; Hultman *et al*, 1997), unaffected siblings (Lane & Albee, 1966; Woerner *et al*, 1971) and individuals with an affective psychosis (Rifkin *et al*, 1994). However, there are also many studies reporting no significant difference in birthweight between patients with schizophrenia

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Table 1 Obstetric complications found to be more common in patients with schizophrenia

Study	Obstetric complications
McNeil & Kaij (1978)	Pre-eclampsia, inertia of labour
Jacobsen & Kinney (1980)	Long labour
Parnas *et al* (1982)	Bad foetal position
Eagles *et al* (1990)	Premature rupture of membranes
O'Callaghan *et al* (1992)	Foetal distress
Stöber *et al* (1993)	Maternal infectious diseases during mid-gestation
Günther-Genta *et al* (1994)	Umbilical cord complications, atypical presentations
Rifkin *et al* (1994)	Low birthweight
Kendell *et al* (1996)	Pre-eclampsia
Hultman *et al* (1997)	Disproportionate birthweight for body length, small head circumference
Jones *et al* (1998)	Low birthweight
Dalman *et al* (1999)	Pre-eclampsia
Hultman *et al* (1999)	Multiparity, maternal bleeding during pregnancy

and their healthy siblings, normal controls or live births (Pollack *et al*, 1966; Jacobsen & Kinney, 1980; McCreadie *et al*, 1992; O'Callaghan *et al*, 1992; Günther-Genta *et al*, 1994; Kendell *et al*, 1996, 2000; Jones *et al*, 1998). Thus it is not clear-cut as to whether mean birthweight is lower in patients with schizophrenia than in control subjects.

If schizophrenia could be placed within a continuum of reproductive causality from neonatal death, through cerebral palsy to behaviour disorders, as Pasamanick *et al* (1956) proposed, then the frequency of low birthweight rather than mean birthweight might be more important, since low birthweight is a more clearly defined risk factor for cerebral palsy. Using Medline, we searched for recent studies comparing the frequency of low birthweight (<2500 g) between patients with schizophrenia and controls; six studies were found that were published in the 1990s. These studies and our own more recent data (Ichiki *et al*, 2000) are shown in Table 2. A significantly increased frequency of low birthweight among patients with schizophrenia compared with controls was reported in five out of the seven studies. The odds ratios in six out of the seven studies ranged between 1.7 and 3.9. The overall pooled data yielded a highly significant result: 9.5% and 3.9% of approximately 750 patients with schizophrenia and 29 000 control subjects respectively were born with low birthweight ($P<0.00001$, by Fisher's exact test, two-tailed, odds ratio 2.6, 95% CI 2.0–3.3). This indicates that low birthweight is a modest – but definite – risk factor for adult schizophrenia.

Twin studies

Since monozygotic (MZ) twins share the same genetic material, it is advantageous to investigate intra-pair differences in birthweight for MZ twins discordant for schizophrenia in order to determine the effect of birthweight on the development of the illness. Pollin & Stabenau (1968) analysed 100 pairs of MZ twins discordant for schizophrenia or severity of schizophrenia and provided evidence of lower birthweight in the twins with schizophrenia than in their co-twins. In contrast, Gottesman & Shields (1976), who examined 82 pairs from five studies, reported lower birthweight to be equally distributed among twins with schizophrenia and their well co-twins. However, Torrey (1977), who re-examined the same data, excluding partially concordant pairs, concluded that lower birthweight was more frequent in the affected twins than in the unaffected co-twins.

Table 2 Studies comparing the frequency of low birthweight in patients with schizophrenia and control subjects

Study	Schizophrenia group		Control group		Odds ratio (95% CI) and *P* value	Comment
	n	LBW[1]	*n*	LBW[1]		
Ichiki *et al* (2000)	312	30 (9.6%)	517	24 (4.6%)	2.2 (1.3–3.8) $P=0.005$	Japanese case–control study
Dalman *et al* (1999)	238	16 (6.7%)		Data not shown	1.7 (1.0–3.0)	Swedish cohort study
Hultman *et al* (1999)	167	11 (6.6%)	835	31 (3.7%)	1.8 (0.9–3.7)[2] $P=0.09$[2]	Swedish cohort study
Jones *et al* (1998)	76	6 (7.9%)	10 498	360 (3.4%)	2.4 (1.0–5.6) $P=0.03$	Finnish cohort study
Sacker *et al* (1995)	49	7 (14.7%)	16 812	706[2] (4.2%)	3.9 (1.9–8.1) $P<0.01$	British cohort study; schizophrenia was narrowly defined by PSE category
Rifkin *et al* (1994)	100	15[2] (15%)	67	1[2] (2%)	11.6 (1.5–90.4)[2] $P=0.002$[2]	British case–control study. Controls were patients with affective psychosis
Heun & Maier (1993)	43	2 (4.7%)	74	2 (2.7%)	1.8 (0.2–12.9)[2] $P=0.62$[2]	German case–control study. Controls were siblings of subjects with schizophrenia
Total[3]	747	71 (9.5%)	28 803	1124 (3.9%)	2.6 (2.0–3.3) $P<0.00001$	

PSE; Present State Examination.
1. Low birthweight (LBW) defined as a weight less than 2500 g.
2. Calculated or estimated by the authors.
3. The study of Dalman *et al* (1999) was not included because they did not describe the number or frequency of individuals with low birthweight among their control subjects.

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More recently Onstad *et al* (1992) examined 16 MZ twin pairs discordant for schizophrenia, and found that there was no significant difference in mean birthweight between those with schizophrenia and the unaffected twins. McNeil *et al* (1994), who investigated 23 MZ twin pairs discordant for schizophrenia, reported that birthweight was not significantly lower in the twins with schizophrenia than in the well co-twins.

To summarise the data from studies on MZ twin pairs discordant for schizophrenia, there is no clear-cut evidence for lower birthweight in twins with schizophrenia when compared with their unaffected co-twins. However, the sample sizes were too small to detect the possible weak relationship between mean birthweight and the development of schizophrenia. Furthermore, given the sample sizes, it is difficult to draw any conclusion with respect to the relationship between low birthweight and subsequent schizophrenia. Another limitation was that most twin studies obtained their obstetric data from maternal or other relatives' recall rather than from hospital records.

Head circumference at birth

McNeil *et al* (1993) found a reduced head circumference at birth in patients with schizophrenia compared with controls. Subsequently, Kunugi *et al* (1996*b*) found a smaller head circumference at birth for gestational age in patients with schizophrenia compared with controls. Hultman *et al* (1997) also provided evidence for smaller head circumference at birth in patients with schizophrenia.

These findings are intriguing since some studies reported that patients with schizophrenia have reduced whole-brain (especially cortical) volume (Zipursky *et al*, 1992; Harvey *et al*, 1993). These structural changes are thought to be non-progressive, and to originate early in life (Roberts, 1991; Murray, 1994). Since head circumference accurately reflects intracranial volume (Bray *et al*, 1969) and correlates with the number of cells in the brain (Winick & Rosso, 1969), smaller head circumference at birth might reflect primary neurodevelopmental impairment in schizophrenia dating from the prenatal period. Small head size at birth was shown to be a predictor of neurological impairments and lower IQ at the age of 5 years among low-birthweight infants (Gross *et al*, 1978).

PRENATAL UNDERDEVELOPMENT AND BRAIN DAMAGE

Figure 1 illustrates mechanisms that may underlie the possible association between prenatal underdevelopment and central nervous system (CNS) damage. Genetic predisposition to schizophrenia may be associated with lower birthweight. In accordance with this, Mednick *et al* (1971), in their Danish high-risk sample, reported that children born to a parent with schizophrenia evidenced a higher incidence of mildly low birthweight. Although McNeil & Kaij (1973) did not find a significantly lower mean birthweight in the offspring of mothers with schizophrenia than those of control mothers, more of the former were small for their gestational age. The Jerusalem Infant Development Study (Marcus *et al*, 1981) showed that infants born to patients with schizophrenia tended to have low to low-normal birthweights. More recently, Bennedsen *et al* (1999) investigated the offspring of 1537 women with schizophrenia, and found that pre-term birth, low birthweight and being small for gestational age were significantly more common in the offspring of women with schizophrenia, compared with those of control mothers.

Pregnancy complications such as malnutrition, smoking, pre-eclampsia and diseased placenta are known to be associated with lower birthweight (Lubchenco, 1975). These environmental insults may cause chronic hypoxia in the foetus with resultant abnormalities in the CNS. Intriguingly, Wright *et al* (1995) found that maternal influenza infection during the second trimester was associated with lower birthweight in the offspring. This may account, at least in part, for a possible mechanism underlying the relationship between maternal influenza and adult schizophrenia (e.g. Mednick *et al*, 1988; O'Callaghan *et al*, 1991; Kunugi *et al*, 1995).

Furthermore, several perinatal complications secondary to low birthweight or premature birth are likely: respiratory failure, jaundice leading to kernicterus, dyshaemopoietic anaemia and infectious diseases, for example. Small infants do not tolerate labour and delivery well, and may suffer foetal distress and aspiration of meconium. Such infants have also an inability to conserve heat, and hypoglycaemia is frequently observed (Lubchenco, 1975). All these untoward conditions are likely to have detrimental effects on brain development in the perinatal period. Additional primary perinatal complications such as premature rupture of membranes, umbilical cord complications, inertia of labour and prolonged labour may also cause hypoxia and ischaemic brain damage.

In severe cases, prematurity is often complicated by intraventricular haemorrhagic infarction and periventricular leucomalacia, which are associated with

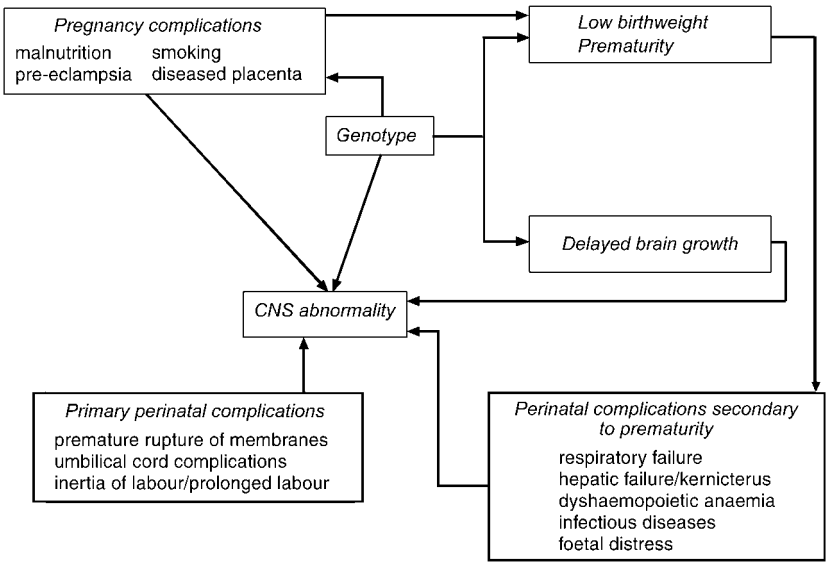

Fig. 1 Possible mechanisms underlying the link between low birthweight and central nervous system (CNS) damage.

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subsequent neurological handicaps such as cerebral palsy and less prominent developmental disabilities of motility, cognition and behaviour (Vohr & Ment, 1996; Volpe, 1997). It is an open question whether milder forms of these pathological conditions are related to schizophrenia.

PREMATURITY AT BIRTH AND SUBSEQUENT NEURODEVELOPMENTAL ABNORMALITIES: IMPLICATIONS FOR SCHIZOPHRENIA

In the general population, low birthweight is a risk factor for major neurological impairments, such as cerebral palsy, significant developmental delay and sensory deficits, particularly in very low-birthweight (<1500 g) infants. Even when such major impairments do not occur, low birthweight is also associated with reading difficulties, language delay, poor visual motor integration, behavioural problems and lower IQ at school age (Aylward *et al*, 1989; Lukeman & Melvin, 1993). These neurodevelopmental abnormalities are attributable to perinatal brain damage. Stewart *et al* (1999), who examined magnetic resonance imaging (MRI) scans of adolescents who had been born very preterm, found that more than half of such individuals had abnormalities of ventricles, corpus callosum and white matter, and that reading, adjustment and neurological impairments were related to the brain abnormalities.

These observations in the general population led to the hypothesis that a subgroup of patients with schizophrenia who were subject to prenatal underdevelopment might show neurodevelopmental abnormalities from early in life. Indeed, Rifkin *et al* (1994) found that lower birthweight correlated significantly with poorer premorbid social and cognitive ability among patients with schizophrenia. Cannon *et al* (1997) obtained further evidence for lower birthweight correlating with poorer premorbid adjustment in terms of sociability and schooling. Fish *et al* (1992) found in their Jerusalem Infant Development Study that there was a negative correlation between birthweight and motor development at 10 years of age in the offspring of mothers with schizophrenia. Torrey *et al* (1994), who examined 23 pairs of MZ twins discordant for schizophrenia, found that there were two subgroups of early and late divergence groups. In the early divergent group, the affected and unaffected twins became permanently different from each other in motor skills or unusual behaviour at the age of 5 years or before. Of note is the fact that in all the twin pairs with an intra-pair birthweight difference of 20% or more, the twin who became ill was the lighter one and had an early age of divergence.

All these observations support the possibility that a subgroup of patients with schizophrenia suffer prenatal underdevelopment and this group tends to show poor premorbid functioning.

PERINATAL BRAIN DAMAGE AND SCHIZOPHRENIA

If a portion of schizophrenia originates from prenatal underdevelopment and associated perinatal brain damage, then there should be a correlation between prenatal underdevelopment and morphological changes of the brain in patients with schizophrenia. Although numerous studies investigated structural brain abnormalities in schizophrenia, few have examined the possible relationship between prenatal development and brain morphology in schizophrenia. In the Danish high-risk study, lower birthweight was associated with ventricular enlargement and periventricular damage in a sample genetically predisposed to schizophrenia (Silverton *et al*, 1985; Cannon *et al*, 1989). In contrast, Mukherjee *et al* (1993) did not find such a relationship in chronic patients with schizophrenia. These studies were limited by the use of X-ray computerised tomography rather than MRI in measuring brain structures. In addition, the study of Mukherjee *et al* (1993) was inadequate in sample size (n=24) to detect a moderate effect size. Further studies using MRI in larger sample sizes are needed to clarify the relationship between prenatal underdevelopment and structural brain abnormalities in schizophrenia.

CONCLUSION

We looked at the possible aetiological role of prenatal underdevelopment in schizophrenia. Pooled data from the recent world literature showed that low birthweight (<2500 g) is a modest, but definite, risk factor for schizophrenia. Thus, in a small proportion of patients, schizophrenia appears to originate from perinatal hypoxic brain damage associated with prenatal underdevelopment. This subgroup tends to show poorer premorbid psychosocial functioning, and might be placed within the continuum of reproductive casualty from cerebral palsy to behaviour disorders, which Pasamanick *et al* (1956) proposed. To elucidate this issue, studies are needed to examine the possible relationship between prenatal underdevelopment and structural and functional abnormalities of the brain in schizophrenia.

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