Labour and delivery complications and schizophrenia

Case–control study using contemporaneous labour ward records

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Background Controversy continues regarding an association between obstetric complications and risk of schizophrenia in early adult life.

Aims To compare the rate of labour and delivery complications among persons who developed schizophrenia with controls; to establish whether any complication is associated with later schizophrenia.

Method We located the labour ward records of 431 individuals with schizophrenia and of same-gender controls from the same hospital birth series. Mothers were matched by age, socio-economic group and parity. Individual complications were evaluated blindly using two obstetric complication scales.

Results Overall, the rate of labour and delivery complications for those who developed schizophrenia did not differ from that of controls. Males who had presented to psychiatric services before the age of 30 had a greater frequency of and more severe labour/delivery complications than their matched controls.

Conclusions Other than among young-onset males we found no increase in labour and delivery complications among cases.

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Although a genetic basis for schizophrenia is now virtually undisputed (Cardno *et al*, 1999), cohort studies have provided evidence both for (Hultman *et al*, 1997; Jones *et al*, 1998; Dalman *et al*, 1999) and against (Done *et al*, 1991; Buka *et al*, 1993) an association between obstetric adversity and later development of the disease. In a meta-analysis, Geddes & Lawrie (1995) concluded that while there was some evidence of an association, there was also evidence for publication bias, as relatively few small negative studies had been published. Many studies within that meta-analysis had small numbers of index cases, relied on maternal recall of obstetric complications and failed to control for social class at the time of birth. We set out to address some of these methodological difficulties by using contemporaneous birth records of patients from a geographically defined case register and closely matched controls.

METHOD

Subjects

The Dublin Psychiatric Case Register is based on an integrated community service for a population of approximately 253 000. A specialist team compiles data for all in-patient and out-patient contacts with the psychiatric services. We initially selected 1779 Dublin-born patients who had been given an ICD–9 (World Health Organization, 1978) diagnosis of schizophrenia (ICD–9 295.0–295.9) between 1972 and 1992. Four hundred and thirty-one cases were included in the final analyses. The reasons for excluding cases are shown in Table 1.

Birth records

The maternity hospital labour ward diary detailed the following: parental names; age of mother; parity, number of pregnancies, length of gestation; paternal occupation; gender of child; date of birth; mode of delivery; presentation; whether twin or singleton; birth weight; premature rupture of membranes; nature of labour; hours in labour; child's and mother's health immediately after delivery; transfer to baby unit; immediate baptism. The diary, including a free-text record of the birth and delivery, was recorded verbatim. Similar data relating to home births, including a 9-day follow-up record of the baby's health, were also recorded.

Controls

The previous same-gender singleton live birth recorded in the labour ward diary, matched for maternal age, parity, social class and home/hospital birth, was selected as a control. The maternal age of the index case ± 2 years was chosen as the age cut-off point for the maternal control. Parity status was classified as follows: prima gravida (first delivery), multi gravida (2–4 deliveries) or grand multi gravida (more than four deliveries). Social class, based on paternal occupation, was matched according to the classification system of O'Hare *et al* (1991), which is also used by the Irish Central Statistics Office. One of the hospitals did not record paternal occupation, so where possible we obtained this information from the General Register Office birth register. Because we were unable to establish whether controls lived to the age at which the risk of developing schizophrenia occurs, we identified 22 deaths in the first year of life in the General Register Office death register and replaced them with appropriate controls. All birth records were rated blindly according to two obstetric complication scales, scale 1 (Lewis *et al*, 1989) and scale 2 (Parnas *et al*, 1982).

Analyses

Individual items from the obstetric complication scales were analysed separately using matched pairwise techniques. Odds ratios (ORs) and confidence intervals (CIs) were calculated for binary variables. Conditional logistic regression was used to compute for the development of the disorder after allowing for case–control matching. This procedure was repeated for each of the items in the separate scales.

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Table 1 Case tracing results

	Cases lost to sample	Sample size (*n*)	Percentage of sample that are searchable singleton maternity hospital births
Register	–	1779	–
Insufficient register data to allow tracing	349	1430	–
Estimate of sample not born in study hospitals (19.8%)	283	1147	–
Twin births	40	1107	–
Found cases	–	541	49%
Missing social class data for matching	110	431	39%

Percentages are based on singleton births available to study.

Table 2 Matching criteria: a comparison of cases and controls (n=431)

Criterion	Cases	Controls	*T* or *z*	*P*
Maternal age (years)	30.7 (s.d.=5.9)	30.6 (s.d.=5.8)	T=0.88	0.38[1]
Number of pregnancies	3.98 (s.d.=2.9)	3.91 (s.d.=2.9)	T=−0.78	0.44[1]
Social class	4.98 (s.d.=1.2)	4.98 (s.d.=1.2)	z=−0.02	0.98[2]

1. Paired *t*-tests.
2. Mann–Whitney *U*-test.

RESULTS

The final study group comprised 431 cases (256 males, 175 females). This group had fewer married females and fewer in the higher social classes than the original selection. Cases were indistinguishable from controls in terms of maternal age, maternal parity and social class of origin (Table 2).

Scales

Cases did not differ from controls on scale 1 in terms of either definite (OR 1.05, 95% CI 0.72–1.54, P=0.85) or equivocal (OR 0.92, 95% CI 0.61–1.40, P=0.76) complications. Because we were evaluating contemporaneous labour ward records rather than depending on maternal recall, we also combined the definite and equivocal complications categories and found no difference between patients and controls. Similarly, scale 2 did not distinguish between cases and controls in terms of frequency, severity or total complications score.

In the light of previous findings (O'Callaghan *et al*, 1992; Kirov *et al*, 1996; Verdoux *et al*, 1997; Smith *et al*, 1998) we split the study groups by age at first diagnosis and gender and found that only males diagnosed with schizophrenia before the age of 30 (Table 3) had a greater number of definite complications than controls on scale 1. Similarly, using scale 2, male patients had a higher frequency of and more severe complications than their matched controls (Table 4).

Individual complications

The specific complications of Caesarean section (OR 4.00, 95% CI 1.08–22.1, P=0.04) and narrow pelvis (OR 7.00, 95% CI 0.90–320, P=0.07) distinguished patients from controls. The individual complications, classified by gender and age of presentation, for each scale are shown in Tables 5 and 6. We found that Caesarean section (both emergency and not otherwise specified (NOS)) distinguished between cases and controls (OR 7.82×10^{14}, 95% CI 0–0, P=0.004) and was specific to males. Those born by Caesarean section presented to the psychiatric services at a significantly younger age (mean 24.01 years, s.d.=6.3; T=3.76, P=0.003) than those born by normal delivery (mean 31.4 years, s.d.=10.6). Conditional logistic regression analysis of the males confirmed that only Caesarean section was significant (log likelihood removal = 354.9, d.f.=1, $P \leqslant 0.001$) in differentiating between cases and controls. For females, only low birth weight (log likelihood removal = 242.6, d.f.=1, P=0.002) distinguished between the two groups.

Table 3 Obstetric complication scale 1: summary scores (Lewis & Murray, 1989)

Scale 1	Males			Females		
	Cases	Controls	OR (95% CI)[1]	Cases	Controls	OR (95% CI)[1]
Total						
Definite complication[2]	50:206	37:219	1.41 (0.88–2.27)	22:153	32:143	0.64 (0.36–1.16)
Equivocal complication	51:205	46:210	1.13 (0.70–1.81)	19:156	28:147	0.56 (0.26–1.20)
Any complication[3]	84:172	74:182	1.21 (0.81–1.83)	35:140	52:123	0.53 (0.30–0.94)*
Cases presenting at age <30 years						
Definite complication	36:105	19:122	2.27 (1.12–4.62)*	14:70	18:66	0.85 (0.38–1.89)
Equivocal complication	36:105	35:106	0.95 (0.56–1.93)	10.74	12:72	0.83 (0.25–2.73)
Any complication	59:82	45:96	1.61 (0.89–2.90)	19:65	26:58	0.69 (0.30–1.62)

1. Cases *v.* controls.
2. Definite and equivocal complications as per scale of Lewis *et al* (1989).
3. Any complication: combined definite and equivocal scores.
* P<0.05.

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Table 4 Obstetric complication scale 2: summary scores (Parnas *et al*, 1982)

Scale 2	Males		Females	
	z	*P*	z	*P*
Total				
Frequency of complications[1]	−2.05	0.04	−0.68	0.50
Severity score	−1.46	0.15	−0.60	0.55
Total score	−1.60	0.11	−0.38	0.71
Cases presenting at age <30 years				
Frequency of complications	−2.46	0.01	−0.91	0.36
Severity score	−2.06	0.04	−0.74	0.46
Total score	−2.19	0.03	−0.71	0.48

1. Frequency score based on scale of Parnas; severity score rated according to scale; total score – combined severity scores for each complication present. Wilcoxon matched pair signed rank tests of cases *v.* controls.

DISCUSSION

Limitations

The patients received a clinical discharge diagnosis by a psychiatrist according to ICD–8 (World Health Organization, 1974) or ICD–9 rather than a research diagnosis. Less than 50% of the targeted sample were found, more male than female birth records were identified and the age at first diagnosis was younger for located cases. These results could be accounted for by our inability to trace the birth records of married females. Some home births were excluded because their records contained insufficient detail. Social class is related to obstetric outcome (Wilcox *et al*, 1995), so we excluded 110 cases that could not be matched adequately for social class of origin. Finally, the labour ward diaries contained only limited information on early pregnancy and the postnatal period.

Scales and individual labour and delivery complications

Despite applying two frequently used obstetric complication scales we failed to find differences between cases and controls in terms of overall complication scores. There is an apparent difference between these overall results and other large studies in this field (Kendell *et al*, 1996; Hultman *et al*, 1997). One potential explanation for the contradictory results may lie in the patient selection procedures. Many case–control and cohort studies (Done *et al*, 1991; McCreadie *et al*, 1992; Verdoux & Bourgeois, 1993; Kendell *et al*, 1996) have relied on information from patients born in recent years when either their mothers were alive or birth records, particularly computerised information, were available. Such patients are more likely to have had a young age at onset. While this study indicates that young male patients do have an excess of obstetric complications we failed to find any general effect of obstetric adversity among persons developing the disorder.

Persons who later developed schizophrenia were more likely to have been born by Caesarean section. This finding complements those of the recent meta-analysis by Verdoux *et al* (1997) and a National Register study in Denmark (Bennedsen *et al*, 1998), although in the present study the effect was confined to males. We confirm, using a case register study, the meta-analysis result (Verdoux *et al*, 1997) that Caesarean section is related to a younger age at first presentation with schizophrenia.

Although this association is interesting, the complication itself is non-specific. Caesarean section is the result of the obstetrician's judgement to intervene in response to a variety of potential risks. Most of the patients in this study were born when the rate of Caesarean section was less than 3% and was rarely an elective procedure. The commonest recorded reasons for section were major antepartum haemorrhage, deep transverse arrest or failure of labour to progress where foetal distress was apparent. Cephalopelvic disproportion was noted in 25% of cases born by Caesarean section, and a clinical note recording 'narrow pelvis' was found more frequently among cases than among controls.

One of the commonest reasons for a narrow maternal pelvis is poor nutrition during adolescence. Mothers born and raised in Third World countries who migrated to the USA are on average shorter and have narrower pelvic dimensions than mothers born in the USA. Those immigrant women who eat a high-protein diet and receive adequate prenatal care give birth to relatively large infants, which results in cephalopelvic disproportion and severe dystocia (Abitbol *et al*, 1997). In addition to the direct effects of malnutrition (Susser & Lin, 1992), cephalopelvic disproportion merits consideration as a nutritionally related risk factor, particularly for groups previously described as having increased risk of schizophrenia (Warner, 1995; Harrison *et al*, 1997).

The reported palatal (O'Callaghan *et al*, 1991; Cantor-Graae *et al*, 1994; Lane *et al*, 1997) and craniofacial abnormalities among patients with schizophrenia may not entirely result from genetic factors, as we considered previously but may be related to a moulding process in a narrow pelvis (de la Fuente, 1991). However, a narrow pelvis in itself does not necessarily result in damage to the foetus, since when identified it commonly results in operative delivery.

Among patients, a gestational age of less than 37 weeks occurred more frequently among males whose first diagnosis was before the age of 30. While this result has been reported previously (Jones *et al*, 1998), such cases, as with Caesarean section and cephalopelvic disproportion, accounted for a modest proportion of our study group. Indeed, despite several individual complications being associated with the later development of schizophrenia, the proportion of cases affected was extremely small, indicating that obstetric adversity is not associated with the majority of cases of schizophrenia, especially when the age at onset is over 30 years.

Although this paper describes a large case–control study which used contemporaneous records, the fact that many individual labour and delivery complications occur at a frequency of less than 10% in the general population suggests that the cross-referencing of population-based obstetric databases with psychiatric case registers is necessary in order to address definitively the contribution of individual complications to the risk of schizophrenia.

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Table 5 Individual complications from scale I (Lewis *et al*, 1989): individual complication odds ratios between cases and controls. Sample divided initially by gender and then by age of presentation to psychiatric services

Complication	Total sample						Case–control pairs presenting at age <30 years					
	Males			Females			Males			Females		
	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)
Definite complications												
Rhesus incompatibility	1:255	0:256	2.9×10^{14} (0–0)	2:173	2:173	1.0 (0.1–16.0)	1:140	0:140	–	1:83	2:82	5.1×10^{-16} (0–0)
Pre-eclampsia severe	3:253	2:254	0.8 (0.2–3.4)	0:175	1:174	1.3×10^{-15} (0–0)	1:140	1:140	1.0 (0.1–16.0)	0:84	0:84	–
Antepartum haemorrhage	3:253	2:254	0.5 (0.1–2.7)	0:175	4:171	1.3×10^{-15} (0–0)*	3:138	3:138	1.0 (0.1–7.1)	0:84	2:82	1.3×10^{-15} (0–0)
Labour >36 h	2:254	3:253	0.5 (0.1–4.0)	2:173	3:172	0.5 (0.1–5.5)	1:140	1:140	1.0 (0.1–16.0)	0:84	1:83	1.3×10^{-15} (0–0)
Labour <3 h	12:244	9:247	1.4 (0.6–3.4)	8:167	10:165	0.8 (0.3–2.1)	9:132	4:137	6.0 (0.7–49.8)*	6:78	4:80	1.3 (0.30–5.96)
Cord prolapse	1:255	2:254	0.5 (0.1–5.5)	2:173	0:175	7.8×10^{14} (0–0)	0:141	1:140	1.3×10^{-15} (0–0)	2:82	0:84	7.8×10^{14} (0–0)
Gestational age <37 weeks	11:245	5:251	2.2 (0.8–6.3)	2:173	5:170	0.4 (0.1–2.1)	9:132	1:140	8.0 (1.0–64.0)*	1:83	3:81	0.3 (0.1–3.2)
Gestational age >42 weeks	3:253	1:255	3.0 (0.3–28.8)	2:173	3:172	0.7 (0.1–4.0)	3:138	1:140	3.0 (0.3–28.8)	1:83	3:81	0.3 (0.1–3.2)
Caesarean section (emergency)	5:251	0:256	7.8×10^{14} (0–0)	2:173	2:173	1.0 (0.2–7.1)	5:136	0:141	7.8×10^{14} (0–0)*	1:83	2:82	1.0 (0.1–16.0)
Breech/abnormal presentation	11:245	6:250	1.8 (0.7–5.0)	5:170	9:166	0.6 (0.2–1.7)	7:134	2:139	1.5 (0.3–9.0)	2:82	6:78	0.5 (0.1–2.7)
High/difficult forceps	9:247	9:247	1.0 (0.4–2.7)	3:172	0:175	7.8×10^{14} (0–0)*	6:135	6:135	1.0 (0.3–4.0)	2:82	0:84	7.8×10^{14} (0–0)
Birthweight <2000 g	3:253	1:255	3.0 (0.3–28.8)	0:175	2:173	1.3×10^{-15} (0–0)	1:140	0:141	–	0:84	1:83	4.7×10^{-16} (0–0)
Equivocal complications												
Pre-eclampsia NOS	8:248	6:250	1.4 (0.4–4.4)	2:173	1:174	2.0 (0.2–22.1)	7:134	6:135	2.0 (0.5–8.0)	2:82	1:83	2.0 (0.2–22.1)
Labour >24 h/difficult/precipitate	10:246	11:245	0.9 (0.4–2.1)	3:172	4:171	0.8 (0.2–3.4)	7:134	7:134	0.7 (0.2–2.3)	1:83	1:83	0.6 (0.1–16.0)
Cord knotted around neck	1:255	1:255	1.0 (0.1–16.0)	0:175	1:174	1.3×10^{-15} (0–0)	1:140	0:141	7.8×10^{14} (0–0)	0:84	0:84	–
Premature/postmature	2:254	2:254	1.0 (0.1–7.1)	0:175	2:173	1.3×10^{-15} (0–0)	1:140	1:140	1.00 (0.1–16.0)	0:84	0:84	–
Caesarean section NOS	5:251	0:256	7.8×10^{14} (0–0)	0:175	1:174	3.5×10^{-15} (0–0)	3:138	0:141	7.8×10^{14} (0–0)*	0:84	0:84	–
Forceps/instrumental delivery	15:241	16:240	1.2 (0.6–2.4)	9:166	10:165	1.2 (0.4–3.5)	12:129	14:127	1.0 (0.4–2.5)	3:81	6:78	0.3 (0.1–3.2)
Birth weight <2500 g/small	8:248	7:249	0.7 (0.3–1.8)	2:173	10:165	1.2 (0.0–0.8)*	3:138	3:138	0.4 (0.1–2.1)	2:82	6:78	0.3 (0.1–1.7)
Incubator/resuscitation/blue	14:242	13:243	1.1 (0.5–2.6)	5:170	3:172	1.7 (0.4–7.0)	10:131	10:131	0.9 (0.3–2.6)	2:82	3:81	1.0 (0.1–7.1)
Gross anomaly	2:254	1:255	2.0 (0.2, 22.1)	0:175	1:174	3.5×10^{-15} (0–0)	1:140	1:140	1.0 (0.1–16.0)	0:84	0:84	–

*$P < 0.05$.
NOS, not otherwise stated.

Table 6 Individual complications from scale 2 (Parnas *et al*, 1982): individual complication odds ratios between cases and controls. Sample divided initially by gender and then by age at presentation to psychiatric services

Complication	Total sample						Case–control pairs presenting at age <30 years					
	Males			Females			Males			Females		
	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)
Forceps	23:233	25:231	0.9 (0.5–1.7)	12:163	10:165	1.6 (0.5–4.9)	17:124	19:122	0.8 (0.4–1.7)	5:79	6:78	1.0 (0.1–7.1)
Caesarean section	10:246	0:256	7.8×10^{14} (0–0)*	2:173	3:172	0.7 (0.1–4.0)	8:133	0:141	7.8×10^{14} (0–0)*	1:83	2:82	1.0 (0.1–16.0)
Placental defects	4:252	4:252	1.0 (0.2–3.4)	1:174	3:172	0.3 (0.1–3.2)	3:138	4:137	1.0 (0.1–7.1)	1:83	1:83	1.0 (0.1–16.0)
Previous foetal loss	4:252	5:251	0.8 (0.2–3.4)	5:170	4:171	1.3 (0.3–6.0)	3:138	5:136	0.3 (0.1–2.2)	4:80	4:80	1.0 (0.2–5.0)
Bleeding after delivery	5:251	4:252	1.3 (0.4–4.7)	2:173	0:175	7.8×10^{14} (0–0)	2:139	1:140	2.0 (0.2–22.1)	1:83	0:84	7.8×10^{14} (0–0)
Narrow pelvis	6:250	1:255	6.0 (0.7–49.8)*	1:174	0:175	7.8×10^{14} (0–0)	6:135	0:141	7.8×10^{14} (0–0)*	0:84	0:84	–
Mother's illness during pregnancy	13:243	6:250	2.4 (0.9–6.8)	6:169	7:168	0.9 (0.3–2.6)	9:132	5:136	4.0 (0.9–18.8)*	5:79	5:79	1.0 (0.3–3.5)
Labour time >24 h	5:251	6:250	0.8 (0.3–2.7)	2:173	4:171	0.5 (0.1–2.7)	3:138	2:139	1.5 (0.3–9.0)	0:84	1:83	1.3×10^{-15} (0–0)
Mother's serious illness	2:254	1:255	2.0 (0.2–22.1)	2:173	2:173	1.0 (0.2–7.1)	2:139	1:140	1.0 (0.1–16.0)	0:84	0:84	–
Bad foetal position	11:244	6:250	1.8 (0.7–5.0)	5:170	9:166	0.6 (0.2–1.7)	7:134	2:139	1.5 (0.3–9.0)	2:82	6:78	0.5 (0.1–2.7)
Contractions of pelvis during delivery	0:256	0:256	–	1:174	0:175	7.8×10^{14} (0–0)	0:141	0:141	–	1:83	0:84	–
Primary uterine inertia	1:255	2:254	0.5 (0.1–5.5)	0:175	0:175	–	1:140	2:139	1.0 (0.1–16.0)	0:84	0:84	–
Prematurity with weight >2500 g	8:248	4:252	2.0 (0.6–6.7)	1:174	2:173	0.5 (0.1–5.5)	6:135	0:141	7.8×10^{14} (0–0)*	0:84	0:84	–
Labour time >36 h	2:254	2:254	1.0 (0.2–7.1)	1:174	1:174	1.0 (0.1–16.0)	1:140	1:140	1.0 (0.1–16.0)	0:84	0:84	–
Secondary uterine inertia	9:247	6:250	1.5 (0.5–4.2)	1:174	0:175	2.9×10^{14} (0–0)	6:135	5:136	1.0 (0.3–3.5)	1:83	0:84	7.8×10^{14} (0–0)
Bleeding during delivery	1:255	2:254	3.8×10^{-15} (0–0)	0:175	4:171	1.3×10^{-15} (0–0)*	1:140	1:140	1.4×10^{-15} (0–0)	0:84	3:81	4.7×10^{-16} (0–0)
Labour >48 h	0:256	1:255	3.5×10^{-15} (0–0)	1:174	2:173	0.5 (0.1–5.5)	0:141	0:141	–	0:84	1:83	1.3×10^{-15} (0–0)
Asphyxiation	9:247	6:250	1.6 (0.5–4.9)	2:173	0:175	7.8×10^{14} (0–0)	7:134	4:137	1.7 (0.4–7.0)	0:84	0:84	–
Umbilical complications	2:254	3:253	0.7 (0.1–4.0)	2:173	1:174	2.0 (0.2–22.1)	1:140	1:140	1.0 (0.1–16.0)	2:82	0:84	7.8×10^{14} (0–0)
Eclampsia	2:254	1:255	2.0 (0.2–22.1)	0:175	0:175	–	0:141	0:141	–	0:84	0:84	–
Prematurity with weight <2500 g	4:252	2:254	2.0 (0.4–10.9)	1:174	3:172	0.3 (0.1–3.2)	3:138	1:140	2.0 (0.22–22.1)	1:83	2:82	0.5 (0.1–5.5)

*$P < 0.05$.

Coombe Hospitals) to access labour ward diaries, which have been retained at each hospital since 1896. Additionally, we were granted access to the maternity unit of St James's Hospital which, although no longer functioning as an obstetric unit, has retained some records.

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CLINICAL IMPLICATIONS

- Labour and delivery complications are relevant to some, but certainly not all, patients with schizophrenia.
- Delivery by Caesarean section was more common among patients than controls and was associated with a younger age at first diagnosis among males.
- Male cases were more frequently associated with complications.

LIMITATIONS

- Only 49% of the estimated number of traceable records were found.
- The study was confined to labour and delivery complications. Only limited data for the pregnancies and perinatal period were identified.
- Despite the sample size, we believe that the power of the present study was limited.

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