Labour and delivery complications at birth and later mania

An Irish case register study

ROY BROWNE, MAJELLA BYRNE, NIAMH MULRYAN, ANN SCULLY, MARY MORRIS, ANTHONY KINSELLA, THOMAS F. McNEIL, DERMOT WALSH and EADBHARD O'CALLAGHAN

Background Several reports postulate that manic depression and schizophrenia share environmental risk factors. Although obstetric adversity has been suggested as a risk factor for schizophrenia, few studies have examined its relationship to bipolar affective disorder.

Aims To assess the rate of obstetric complications incurred by patients with mania compared with controls.

Method From the Dublin Psychiatric Case Register we identified individuals with a discharge diagnosis of mania and traced their birth records. Each case was matched with a control of the same gender, born in the same hospital, in the same year, matched for maternal age, parity and social class. Two obstetric complication scales were used to make blind evaluations of labour and delivery data.

Results Patients with mania did not experience a greater frequency or severity of labour and delivery complications than their matched controls. Rates of obstetric adversity were unrelated to the presence or absence of family history of psychiatric disorder. Obstetric adversity was unrelated to the age at first diagnosis.

Conclusions These findings suggest that obstetric adversity is not a risk factor for later mania.

Declaration of interest This study was funded by the Health Research Board, Ireland, and the Stanley Foundation.

Although many researchers have investigated the relationship between obstetric adversity and later schizophrenia (Geddes & Lawrie, 1995), far fewer have examined the relationship between obstetric adversity and later manic depression, and the results have been contradictory (Lewis & Murray, 1987; Done *et al*, 1991; Kinney *et al*, 1993; Verdoux & Bourgeois, 1993; Stober *et al*, 1997). The relative infrequency of manic depression coupled with the scarcity of contemporaneous birth data make investigating a link with labour and delivery complications difficult, and researchers are often forced to rely upon maternal recall, the validity of which is questionable (Cantor-Graae *et al*, 1998). We sought to establish whether labour and delivery complications are a risk factor for later mania and to address some of the methodological difficulties by recruiting from a catchment area-based case register, using contemporaneously recorded obstetric data.

METHOD

Psychiatric services in Ireland are based on a strict catchment area basis. The Dublin Psychiatric Case Register records all contacts with psychiatric services. Socio-demographic factors, age at first presentation and family history of psychiatric disorder are compiled, together with clinical data. Diagnoses were made by consultant psychiatrists based upon the 9th edition of the *International Classification of Diseases* (ICD–9; World Health Organization, 1978) upon discharge. All persons who met the ICD–9 criteria for 'mania' or 'ever manic' between 1972 and 1986 were included. Age at first presentation was defined as the age at first contact with the register as either an in-patient or an out-patient. Family history was recorded at interview and was classified as present if one or more first-degree relative was diagnosed as having a major psychiatric illness.

We attempted to trace the birth records of patients listed as born in the Dublin area by examining the labour and delivery ward books held by the major Dublin maternity hospitals. A series of birth records for patients with other psychiatric diagnoses was included to ensure that the investigators were blind to diagnosis. The record of labour and delivery for the cases and matched controls from the same birth series was recorded verbatim (R.B., M.B., A.S., N.M.). Each district (non-hospital) birth was matched with data for a district control birth. All cases were matched for gender of infant, maternal age (within 2 years) and maternal parity (primagravida, 2–4 deliveries or >4 deliveries). Matching for social class of origin was based on paternal occupation, using the Irish population census-based classification (O'Hare *et al*, 1991). We identified 230 cases with a diagnosis of mania. Birth records were retrieved for 94 cases (41%), 18 of whom were excluded because social class matching proved impossible, leaving a study sample of 76 cases and matched controls.

Each birth record contained substantial information on the labour and delivery but data about the very early stages of pregnancy were of variable quality. Data were rated blindly by E.O'C. using two complication scales that have been described in detail elsewhere (Parnas *et al*, 1982; Lewis *et al*, 1989). The Lewis and Murray Scale (scale I) categorises patients into one of three groups: no complications, equivocal complications or definite complications. The scale of Parnas and colleagues (scale II) derives a frequency, severity and total complication score based on combining severity scores for individual complications. Analyses of these scores were carried out using the Wilcoxon matched-pair signed rank test for summary scores from scale II; odds ratios (OR) were calculated for dichotomous variables between matched case–control pairs, two-sample Student's *t*-tests were used in comparisons of continuous data and χ^2 tests were used to compare discrete data.

RESULTS

We identified the birth records of 76 (24 male, 52 female) individuals and matched these with controls. These cases did not differ statistically from those cases that we were unable to locate or unable to match on the basis of social class in terms of age, gender, age at first presentation to

https://doi.org/10.1192/bjp.176.4.369 Published online by Cambridge University Press

psychiatric services or family history of major psychiatric illness.

At the time of the birth of the index cases, the mothers' mean age was 30 years (s.d.=6.6) and they had a mean of four (s.d.=3.1) previous pregnancies. There was no significant difference ($T=-0.6$, $P=0.5$, 95% CI=−2.4 to 1.2) in the gestational age (weeks) of cases (mean=39.05; s.d.=6.0) compared with controls (mean=39.63; s.d.=1.4). In the total sample the OR for definite complications (Table 1, scale I) was 0.8 ($P=0.8$, 95% CI=0.3–2.3) and for equivocal complications was 2.0 ($P=0.30$, 95% CI=0.6–7.5). Scale I was designed for evaluating birth histories using maternal recall rather than contemporaneous birth records, thus we combined the definite and equivocal sections of the scale to form an 'any complication' group for which the OR was 1.3 ($P=0.7$, 95% CI=0.5–3.1). Male cases did not experience significantly more 'definite' complications (OR=0.7, $P=1.0$, 95% CI=0.1–5.8), 'equivocal' complications (OR=1.0, $P=1.0$, 95% CI=0–78.1), or 'any complication' (OR=1.0, $P=1.0$, 95% CI=0.1–7.5) than their matched controls. Similarly, the birth histories of females who later developed mania did not differ significantly from their matched controls, the ORs being 0.9 ($P=1.0$, 95% CI=0.2–3.0), 1.8 ($P=0.4$, 95% CI=0.5–6.8) and 1.38 ($P=0.7$, 95% CI=0.5–3.9), respectively. The results for scale II (given in Table 2) mirror the scale I results, with no significant increase in the frequency ($z=-0.5$, $P=0.6$), severity ($z=-0.3$, $P=0.8$) or total ($z=-0.5$, $P=0.7$) scores of the complication rates.

Data relating to family history were missing for 14 patients. The 41 patients without a family history of psychiatric disorder did not experience significantly more labour and delivery complications than the 21 patients who had a family history (scale I: $\chi^2=0.7$, 1 d.f., $P=0.4$; scale 2: $\chi^2=1.1$, 1 d.f., $P=0.3$). Finally, the patients with a history of obstetric complications (mean=33.7, s.d.=10.0) did not differ significantly ($T=-1.4$, $P=0.2$, 95% CI=−11.3 to 2.3) in their age at first presentation to psychiatric services from patients without a history of obstetric adversity (mean=38.0, s.d.=15).

DISCUSSION

Methodological considerations

The sample

Although this study has the advantage of being case register-based from a defined geographical area, including both in- and out-patient contacts and using contemporaneous birth records with closely matched controls, there are several methodological limitations. Diagnoses are based on conventional consultant clinical discharge diagnoses rather than research diagnoses using a formal diagnostic interview schedule.

Table 1 Summary scores for scale I (Lewis *et al*, 1987) mania *v.* matched controls

	Male			Female		
	Cases	Controls	OR (95% CI)[1]	Cases	Controls	OR (95% CI)[1]
Total sample						
Definite complication	3/24 (12.5%)	4/24 (16.7%)	0.67 (0.1–5.8)	6/52 (11.5%)	7/52 (13.5%)	0.9 (0.2–3.0)
Equivocal complication	1/24 (4.2%)	0/24 (0%)	1.0 (0.0–78.1)	9/52 (17.3%)	5/52 (9.6%)	1.8 (0.5–6.8)
Any complication	4/24 (16.7%)	4/24 (16.7%)	1.0 (0.1–7.5)	13/52 (25%)	10/52 (19.2%)	1.4 (0.5–3.9)
Cases presenting at age <30 years						
Definite complication	0/3 (0%)	1/3 (33%)	1.0 (0–39.0)	2/18 (11.1%)	3/18 (16.7%)	0.7 (0.1–5.8)
Equivocal complication	0/3 (0%)	0/3 (0%)	Not calculable	4/18 (22.2%)	2/18 (11.1%)	2.0 (0.3–22.1)
Any complication	0/3 (0%)	1/3 (33%)	1.0 (0–39.0)	5/18 (27.8%)	4/18 (22.2%)	1.5 (0.2–17.9)

1. Odds ratios and 95% confidence intervals for cases *v.* controls.

Table 2 Summary scores for scale II (Parnas *et al*, 1982) mania *v.* controls[1]

	Both genders ($n=76$)				Males ($n=24$)				Females ($n=52$)			
	Mean (s.d.) cases	Mean (s.d.) controls	*Z*	*P*	Mean (s.d.) cases	Mean (s.d.) controls	*Z*	*P*	Mean (s.d.) cases	Mean (s.d.) controls	*Z*	*P*
Total sample												
Frequency of complications	0.3 (0.5)	0.3 (0.6)	−0.5	0.6	0.1 (0.3)	0.01 (0.2)	−0.5	0.6	0.3 (0.6)	0.4 (0.8)	−0.5	0.6
Severity score	0.3 (0.8)	0.3 (0.8)	−0.3	0.8	0.2 (0.6)	0.04 (0.2)	−0.3	0.8	0.4 (0.8)	0.5 (0.9)	−0.3	0.7
Total score	0.4 (1.1)	0.4 (1.0)	−0.5	0.7	0.2 (0.6)	0.04 (0.2)	−0.5	0.7	0.5 (1.3)	0.6 (1.1)	−0.5	0.7
	Both genders ($n=21$)				Males ($n=3$)				Females ($n=18$)			
Case presenting at age <30 years												
Frequency of complications	0.4 (0.7)	0.4 (0.8)	−0.1	1.0	0	0.3 (0.6)	−0.1	1.0	0.4 (0.7)	0.4 (0.9)	−0.1	1.0
Severity score	0.5 (0.9)	0.5 (1.0)	0.0	1.0	0	0.3 (0.6)	0.0	1.0	0.6 (1.0)	0.5 (1.1)	0.0	1.0
Total score	0.6 (1.1)	0.5 (1.1)	−0.1	0.9	0	0.3 (0.6)	−0.1	0.9	0.7 (1.2)	0.6 (1.2)	−0.1	0.92

1. Scale II Wilcoxon matched-pair signed rank tests of cases *v.* controls.

https://doi.org/10.1192/bjp.176.4.369 Published online by Cambridge University Press

Only 41% of the original sample were included in the final analyses because many records were not traceable and a considerable proportion of those that were located were not utilised because we could not find data relating to the mothers' social class of origin. These cases were excluded because there is evidence that social and economic adversity are major factors in determining obstetric outcome (Wilcox *et al*, 1995). Although excluded cases did not differ from the final sample in terms of maternal age, parity, gestational age, family history of psychiatric illness or age at first presentation to psychiatric services, the attrition rate of 59% is disappointing.

Obstetric data and rating scales

The birth records that we studied were heavily weighted on the labour and delivery issues, therefore we could not determine the rate of either *in utero* infections or nutritional deprivation. Furthermore, we could not rule out the possibility of unrecorded major early pregnancy complications, although their consequences are often reflected during labour or early after delivery. Additionally, rating scales, by their nature, influence the likelihood that particular items are categorised as either normal or abnormal. McNeil *et al* (1994) evaluated a single data set from a schizophrenia sample using a variety of scales and found differing results that were attributable to scale effects. To minimise such effects we used two scales that have been repeatedly applied to patients with schizophrenia and, in most published data, have found differences between cases and controls (Lewis & Murray, 1987; Eagles *et al*, 1990; O'Callaghan *et al*, 1992). Finally, because of power constraints, these results cannot be interpreted as a definitive exclusion of an association between obstetric adversity and later mania. Realistically, many obstetric complications are very rare events and it would require a sample size of tens of thousands of patients to exclude categorically all obstetric complications. Meta-analytical techniques, such as those applied to schizophrenia (Geddes & Lawrie, 1995), would seem also to be appropriate to manic depression, where published study sample sizes are considerably smaller than in schizophrenia studies.

Comparison with other studies

The principal finding is that labour and delivery complications are not more common among patients who later develop mania than among closely matched controls. Our negative findings contrast with the result of Kinney *et al* (1993), who found an increased frequency and severity of labour and delivery complications among 16 individuals with manic depression compared with their unaffected siblings. It also differs from the results of Lewis & Murray (1987), who reported a modest excess of obstetric adversity among those with manic depression. However, their control group comprised patients with neurotic disorders and the obstetric data were largely abstracted from conventional psychiatric case notes. Although Done *et al* (1991) found no excess of labour or delivery complications, they reported a shortened period of gestation for the 32 individuals who subsequently developed major affective disorder. This was not a predicted finding and this prospective study based on the British perinatal mortality sample found no other indices of perinatal suboptimality; indeed, the cohort of those with schizophrenia were also found to have no significant history of perinatal complications when compared with controls. Hultman and colleagues, in a crossed register study of schizophrenia, affective psychosis and reactive psychosis, with no access to individual birth records, had an ICD classification of major complications during birth (Hultman *et al*, 1999). They identified uterine atony as significantly more common in cases with affective psychosis when compared with controls. Our study does not reflect this in overall complication scores.

Guth *et al* (1993) reported increased complication rates in early-onset manic depression; however, Sigurdsson *et al* (1999) found no significant differences between patients with early-onset bipolar depression and controls with unipolar depression in terms of obstetric adversity but found differences in language delay and social development. This concept of linguistic abnormality has been attributed to genetic factors in the area of schizophrenia research (Crow, 1997), and the study by Sigurdsson *et al* (1999) may provide support for a similar mechanism in manic depression that is unrelated to environmental factors. We found no relationship between labour and delivery complications and age at first presentation to the psychiatric services with mania.

Both Verdoux & Bourgeois (1993) and Stober *et al* (1997) also failed to find any increase in labour or delivery complications among those who later developed bipolar affective disorder. Dalen (1965), although his study had no control group, found that patients with a negative family history of major affective disorder experienced more obstetric complications than those with a family history. Conversely, Marcelis *et al* (1998), employing maternal recall, suggest that patients with a positive family history of affective disorder experience more obstetric complications, although no data are presented in this study to indicate whether patients with affective disorder experienced more obstetric adversity than controls. In our study the presence or absence of a family history of major psychiatric history did not influence the likelihood of having labour and delivery complications.

One of the clinical correlates of obstetric complications among patients with schizophrenia is the relationship between obstetric adversity and age at first presentation (O'Callaghan *et al*, 1990, 1992; Verdoux *et al*, 1997); we found no such relationship for patients with mania.

Implications

The evidence for a link between obstetric adversity and later schizophrenia remains controversial (McNeil & Kaij, 1978; Lewis & Murray, 1987; Eagles *et al*, 1990; O'Callaghan *et al*, 1992; Cantor-Graae *et al*, 1994; McNeil *et al*, 1994; Geddes & Lawrie, 1995) and even if, as the balance of evidence suggests, such an association exists, it does not prove causality. The evidence for a link between obstetric adversity and later mania is even more tenuous and the data presented here further weaken it and may point to a distinction between the two disorders, although not necessarily one of aetiological significance. The relative infrequency of particular obstetric complications coupled with the low occurrence of manic depression implies that further register-based case–control studies using comparable rating methods will enhance the possibility, using meta-analytical techniques, of answering this question definitively.

REFERENCES

Cantor-Graae, E., McNeil, T. F., Sjostrom, K., *et al* (1994) Obstetric complications and their relationship to other etiological risk factors in schizophrenia. A case–control study. *Journal of Nervous and Mental Disease*, **182**, 645–650.

https://doi.org/10.1192/bjp.176.4.369 Published online by Cambridge University Press

__, Cardenal, S., Ismail, B., *et al* (1998) Recall of obstetric events by mothers of schizophrenic patients. *Psychological Medicine*, **28**, 1239–1243.

Crow, T. J. (1997) Is schizophrenia the price that Homo sapiens pays for language? *Schizophrenia Research*, **28**, 127–141.

Dalen, P. (1965) Family history, the electroencephalogram and perinatal factors in manic conditions. *Acta Psychiatrica Scandinavica*, **41**, 527–563.

Done, D. J., Johnstone, E. C., Frith, C. D., *et al* (1991) Complications of pregnancy and delivery in relation to psychosis in adult life: data from the British perinatal mortality survey sample. *British Medical Journal*, **302**, 1576–1580.

Eagles, J. M., Gibson, I., Bremner, M. H., *et al* (1990) Obstetric complications in DSM–III schizophrenics and their siblings. *Lancet*, **335**, 1139–1141.

Geddes, J. R. & Lawrie, S. M. (1995) Obstetric complications and schizophrenia: a meta-analysis. *British Journal of Psychiatry*, **167**, 786–793.

Guth, C., Jones, P. & Murray, R. (1993) Familial psychiatric illness and obstetric complications in early-onset affective disorder. A case–control study. *British Journal of Psychiatry*, **163**, 492–498.

Hultman, C. M., Sparén, P., Takei, N., *et al* (1999) Prenatal and perinatal risk factors for schizophrenia, affective psychosis, and reactive psychosis of early onset: case–control study. *British Medical Journal*, **318**, 421–426.

Kinney, D. K., Yurgelun-Todd, D. A., Levy, D. L., *et al* (1993) Obstetrical complications in patients with bipolar disorder and their siblings. *Psychiatry Research*, **48**, 47–56.

Lewis, S. W. & Murray, R. M. (1987) Obstetric complications, neurodevelopmental deviance, and risk of schizophrenia. *Journal of Psychiatric Research*, **21**, 413–421.

__, Owen, M. J. & Murray, R. M. (1989) Obstetric complications and schizophrenia: methodology and mechanisms. In *Schizophrenia: Scientific Progress* (eds S. C. Schulz & C. A. Tamminga), pp. 56–68. Oxford: Oxford University Press.

McNeil, T. F., Cantor-Graae, E. & Sjostrom, K. (1994) Obstetric complications as antecedents of schizophrenia: empirical effects of using different obstetric complication scales. *Journal of Psychiatric Research*, **28**, 519–530.

__ & Kaij, L. (1978) Obstetric factors in the development of schizophrenia: complications in the births of preschizophrenics and in the reproduction by schizophrenic patients. In *The Nature of Schizophrenia* (eds L. C. Wynne, R. L. Cromwell & S. Matthysse), pp. 401–429. New York: Wiley.

Marcelis, M., van Os, J., Sham, P., *et al* (1998) Obstetric complications and familial morbid risk of psychiatric disorders. *American Journal of Medical Genetics*, **81**, 29–36.

O'Callaghan, E., Larkin, C., Kinsella, A., *et al* (1990) Obstetric complications, the putative familial–sporadic distinction, and tardive dyskinesia in schizophrenia. *British Journal of Psychiatry*, **157**, 578–584.

__, Gibson, T., Colohan, H. A., *et al* (1992) Risk of schizophrenia in adults born after obstetric complications and their association with early onset of illness: a controlled study. *British Medical Journal*, **305**, 1256–1259.

CLINICAL IMPLICATIONS

- The study suggests that labour and delivery complications are not a risk factor for later development of mania.
- Labour and delivery complications were not related to either the presence of a major psychiatric disorder in a relative or the age at first presentation of mania.
- These results may point to a difference in the early development of people with mania compared with people with schizophrenia.

LIMITATIONS

- Diagnoses were based on clinical discharge diagnoses rather than structured interview.
- Only 41% of the birth records contained social class data to enable matching. Although excluded cases did not differ from included cases on a variety of obstetric and psychiatric variables, it is possible that a selection bias was introduced.
- The sample size, although large by comparison with many other studies of manic depression, is modest and therefore one cannot exclude the possibility that obstetric complications, particularly rare obstetric events, are associated with some cases of later mania.

ROY BROWNE, MRCPsych, MAJELLA BYRNE, MSc, MARY MORRIS, BSc, EADBHARD O'CALLAGHAN, MD, Cluain Mhuire Community Psychiatric Service; NIAMH MULRYAN, MRCPsych, ANN SCULLY, MRCPsych, St Loman's Hospital; ANTHONY KINSELLA, MSc, Dublin Institute of Technology, Dublin, Ireland; THOMAS F. McNEIL, PhD, Department of Community Medicine, Lund University, Sweden; DERMOT WALSH, FRCPsych, St Loman's Hospital and Mental Health Section, Health Research Board, Ireland

Correspondence: Dr E. O'Callaghan, Cluain Mhuire Community Psychiatric Service, Newtownpark Avenue, Blackrock, County Dublin, Ireland. Tel: 353-1-2833766; fax: 353-1-2833886

(First received 8 February 1999, final revision 21 June 1999, accepted 17 July 1999)

O'Hare, A., Whelan, C. T. & Commins, P. (1991) The development of an Irish census-based social class scale. *Economic and Social Review*, **22**, 135–156.

Parnas, J., Schulsinger, F., Teasdale, T. W., *et al* (1982) Perinatal complications and clinical outcome within the schizophrenia spectrum. *British Journal of Psychiatry*, **140**, 416–420.

Sigurdsson, E., Fombonne, E., Sayal, K., *et al* (1999) Neurodevelopmental antecedents of early-onset bipolar affective disorder. *British Journal of Psychiatry*, **174**, 121–127.

Stober, G., Kocher, I., Franzek, E., *et al* (1997) First-trimester maternal gestational infection and cycloid psychosis. *Acta Psychiatrica Scandinavica*, **96**, 319–324.

Verdoux, H. & Bourgeois, M. (1993) A comparative study of obstetric history in schizophrenics, bipolar patients and normal subjects. *Schizophrenia Research*, **9**, 67–69.

__, Geddes, J. R., Takei, N., *et al* (1997) Obstetric complications and age at onset in schizophrenia: an international collaborative meta-analysis of individual patient data. *American Journal of Psychiatry*, **154**, 1220–1227.

Wilcox, M. A., Smith, S. J., Johnson, I. R., *et al* (1995) The effect of social deprivation on birthweight, excluding physiological and pathological effects. *British Journal of Obstetrics and Gynaecology*, **102**, 918–924.

World Health Organization (1978) *Mental Disorders: Glossary and Guide to their Classification in Accordance with the Ninth Revision of the International Classification of Diseases (ICD–9)*. Geneva: WHO.

https://doi.org/10.1192/bjp.176.4.369 Published online by Cambridge University Press