Medical outcome of pregnancy in women with psychotic disorders and their infants in the first year after birth

LOUISE M. HOWARD, CLAUDIA GOSS, MORVEN LEESE and GRAHAM THORNICROFT

Background There has been little research into the health of infants of women with psychotic disorders.

Aims To investigate the antenatal care of mothers with a history of psychotic disorders, obstetric outcomes and the subsequent health of their babies.

Method A matched, controlled cohort study was carried out using the General Practice Research Database. Women with a history of a psychotic disorder, who gave birth in 1996–1998, were compared with women matched for age and general practice (199 cases and 787 controls) and their infants.

Results Cases had a higher proportion of stillbirths (OR=4.03, 95% CI 1.14–4.25, $P=0.03$) and neonatal deaths ($P<0.001$). There was no difference in gestational age at antenatal booking. Mothers with psychotic disorders were less likely than controls to attend for infant immunisations 90–270 days after birth (RR=0.94, 95% CI 0.88–0.99, $P=0.03$). There was no significant difference in the rates of accidents and hospital contacts for infants.

Conclusions There is an increased risk of stillbirth and neonatal death in women with a history of psychotic disorder, and it is therefore important for health care professionals to focus on optimal obstetric care. The physical health of babies who live with mothers with psychotic disorders is not significantly different from that of matched baby controls.

Declaration of interest None.

Studies suggest that women with schizophrenia start antenatal care later than controls (Goodman & Emory, 1992) and are more likely to have obstetric complications (Sacker *et al*, 1996; Bennedsen, 1998), including foetal and neonatal deaths (Sobel, 1961; Rieder *et al*, 1975; Modrzewska, 1980). However, a large recent study has suggested that there is no significant increase in stillbirths or neonatal deaths (Bennedsen *et al*, 2001). There has also been little research into the subsequent health of the babies of women with psychotic disorders. Few studies have investigated the outcomes in mothers and babies using an epidemiologically representative population of women with a range of psychotic disorders, and there has been no follow-up study investigating infant health in those children who stayed with their biological families. Our specific hypotheses were:

(a) Women with a history of psychosis attend for antenatal booking at a later stage of gestation than women with no history of psychosis.

(b) Women with a history of psychosis have a higher risk of obstetric complications and perinatal deaths compared with women with no history of psychosis.

(c) There is a higher proportion of neonatal and infant deaths in the offspring of mothers with psychotic disorders.

(d) Infants of mothers with psychotic disorders are more likely to have accidental and non-accidental injuries.

(e) Infants of mothers with psychotic disorders are more likely to have contact with accident and emergency departments and have more hospital referrals made by general practitioners.

METHOD

Participants

This study used the General Practice Research Database (GPRD) (Lis & Mann, 1995; Office for National Statistics, 1996; Walley & Mantgani, 1997), which contains data from up to 480 practices in England for 1996–1999. Data recorded include prescription details, clinical events, preventive care provided, specialist referrals, hospital admissions and their major outcomes. Clinical data are stored and retrieved by means of OXMIS (Oxford Medical Information Systems; Perry, 1978) codes (or Read codes in recent years) for diseases which are cross-referenced to the International Classification of Diseases (ICD–9 and ICD–10; World Health Organization, 1978, 1992). The data collected are audited regularly and the participating general practices subjected to a number of quality checks by the Office for National Statistics, including internal validation by cross-checking within practices and by comparisons with national statistics (Lis & Mann, 1995; Office for National Statistics, 1996; Walley & Mantgani, 1997). Only practices that comply with this quality control – i.e. are 'up to research standard' (UTS) – are included on the database. The data are representative of the general population (Office for National Statistics, 1996), although there is a bias towards larger group practices.

Participants designated as 'cases' ($n=199$) were all women aged 15–44 years with a diagnosis of psychotic disorder or a prescription for a neuroleptic depot, an atypical antipsychotic drug or lithium, who had a birth in the years 1996–1998 identified in a previous study (Howard *et al*, 2002). Each case was matched with up to four controls, where possible, to optimise statistical power, given the fixed number of cases and the budgetary and time constraints of the study. Controls ($n=787$) were recruited from women with no history of psychosis, who had had children during the same years, matched for age (±2 years) and general practice. Controls were not found for two cases (one of a woman aged 38 years and the other 45 years); these cases were therefore not included in this study.

Mothers' records are linked to their baby's records on the GPRD through a household number. This was used to identify the babies born to the participants

during the study period. Where there was no baby recorded in the household and no record of stillbirth or neonatal death, babies were traced by sending a questionnaire to the general practitioner to check whether the baby had been removed from the mother at or soon after birth. In addition to the postal request, practices were telephoned up to three times, if necessary, in order to obtain a high response rate.

Potential predictors known to affect obstetric and infant outcomes were taken from records up to 2 years before index delivery where available and included age, active psychiatric illness (any appointment during or before pregnancy, or any admission during pregnancy or taking any psychotropic medication), any medical problems, illicit drug use, any obstetric problems during index pregnancy, oral or parenteral prescribed medication, smoking and alcohol intake during pregnancy. Outcomes for the mother were date of booking and obstetric complications (excluding Apgar scores and birthweight, which are not routinely recorded by general practitioners). Outcomes for the babies in the first year of life were episodes of accidental injury, self-referrals to accident and emergency departments, referrals to hospital out-patient departments, hospital admissions and primary care consultations for common medical conditions and immunisations.

Power calculation

With the sample size available (cases $n=199$, controls $n=787$) and a base rate of 10% of accident and emergency department contacts among control babies over 1 year, rates of 20% among cases would be detectable with power 80%, using a 5% significance level. With a base rate of 7.5% of accidents in the control group babies, a risk ratio of 2.5 could be detected with the same power and significance levels. These calculations are consistent with an assumed intraclass correlation coefficient of 0.1; with cluster size 5, this reduces the effective sample sizes by a 'design effect' of 1.4, to 142 cases and 562 controls.

Statistical methods

All data were analysed using STATA version 6 (StataCorp, 1999). An initial descriptive analysis examined the demographic details of the cohorts; the proportion of substance misusers and smokers;

medical, obstetric and psychiatric histories; and drugs prescribed during pregnancy. Associations between caseness and possible predictors and outcomes were examined. Logistic regression was used to control for confounding variables for dichotomous outcomes, Poisson regression for rates (single event per patient) and negative binomial regression for multiple event data (Long, 1997). The 'cluster' option in STATA was used to account for the effect of correlations within match-groups on estimates of standard errors and significance levels.

RESULTS

Mothers

The age range of women in the cases group was 17–42 years (mean 29.6, s.d. 5.91), and for the controls group it was 18–43 years (mean 29.6, s.d. 5.79). There was no significant difference in follow-up times between cases and controls: range 382–3534 days, mean 2176, s.d. 863 for cases; range 379–4255, mean 2127, s.d. 936 for the controls ($t=-0.67$, $P=0.51$). There was also no significant difference for follow-up times before birth ($t=-1.16$, $P=0.25$) and after birth ($t=-1.35$, $P=0.18$). Twenty-five (13%) case women and 99 (13%) control women left their general practice during the study period.

The 155 women diagnosed as having a psychotic disorder had the following diagnoses: 34 (22%) schizophrenia, 20 (13%) paranoid psychosis, 26 (17%) psychosis not otherwise specified (NOS), 33 (21%) manic–depressive psychosis, 12 (8%) depressive psychosis, 22 (14%) puerperal psychosis, 6 (4%) schizoaffective psychosis, 2 (1%) drug-induced psychosis. Nineteen per cent (146/787) of women in the control group had a psychiatric history; of these, 92% (134) had neurotic depression, 3% (4) anxiety disorder, 1% (1) drug dependence and 5% (7) had an unclear diagnosis. In 72 (36%) cases the participant had had at least one psychiatric out-patient appointment in the 2 years before the pregnancy or during it. Sixteen (8%) cases had a psychiatric admission during pregnancy.

In 15 (8%) cases and 87 (11%) controls ($\chi^2=2.12$, $P=0.12$) the participant had had one or more medical problems in the 2 years before the index delivery. Women identified as cases were less likely to be prescribed anti-asthmatic drugs – 5 (3%) cases compared with 98 (13%) controls

($\chi^2=16.77$, $P<0.001$) – even though there was no difference in recorded asthma: 10 (5%) cases compared with 56 (7%) controls ($\chi^2=1.11$, $P=0.29$).

There was no significant difference in gestational age at booking: 170 (91%) of the cases group and 662 (93%) of the control group booked before 13 weeks' gestation ($\chi^2=1.36$, $P=0.25$). No significant difference was found when gestational age was alternatively dichotomised at 17 weeks ($\chi^2=0.85$, $P=0.36$) or 20 weeks (Fisher's exact test, $P=0.49$). There was therefore no evidence that in this population women in the cases group were less likely to attend for antenatal care, although a member of this group was the only woman to present at term.

Records of alcohol intake during pregnancy were more likely to be missing in cases (182, 92%) than in controls (578, 73%); $\chi^2=29.17$, $P<0.001$. Of women whose alcohol intake was recorded, a significantly greater proportion of cases (5, 29%) than controls (25, 12%) were noted in which the intake was 1 unit or more per week ($\chi^2=4.16$, $P=0.04$). Records of smoking during pregnancy were also more likely to be missing in cases (148, 74%) than in controls (489, 62%); $\chi^2=10.40$, $P<0.001$. Of women whose smoking data were recorded, 12 (24%) of the 51 in the cases group and 37 (12%) of the 298 in the control group were smoking ($\chi^2=4.46$, $P=0.04$). There was no evidence for a difference in illicit drug use during pregnancy: 2 (1%) cases and 1 (0.1%) control; Fisher's exact test, $P=0.11$. In the cases group, 16 women (8%) had a psychiatric admission and 8 women (4%) took an overdose during pregnancy; no member of the control group took an overdose or had an admission.

There was no significant difference between cases and controls in the risk of most individual obstetric complications. However, there were more Caesarean sections among the cases (39, 20%) than in the controls (111, 14%); $\chi^2=3.71$, $P=0.05$. Cases were less likely to have received advice on contraception postpartum than controls: 127 (64%) cases and 605 (77%) controls, $\chi^2=14.16$, $P<0.001$.

There was a significantly greater proportion of stillbirths in the cases (Table 1). In the five cases involved, the diagnoses were schizophrenia (1), schizoaffective disorder (1), psychosis NOS (1), puerperal psychosis predating the index pregnancy

(1) and one which was included owing to previous prescriptions of index medications (as specified in the methods above), although the woman in this case also developed a puerperal psychosis soon after the stillbirth. Using logistic regression with stillbirth as the outcome variable, there was no evidence of confounding by medical problems ($P=0.29$), prescribed medication during pregnancy ($P=0.65$) or any interaction between caseness and age ($P=0.29$).

There were 4 (2%) neonatal deaths in babies of case mothers compared with none in the control group (Table 1). One neonatal death was due to pneumonia; information on the other three deaths was not available. For neonatal deaths the maternal diagnoses were manic–depressive psychosis (1), psychosis NOS (1), paranoid psychosis (1) and unknown diagnosis (1).

Babies

One hundred and seventy-five 'case' babies were identified, including three sets of twins. Six did not have UTS data; therefore there were 163 mother–infant dyads (166 babies). There were 764 'control' babies identified; among these, there were 19 sets of twins and one set of triplets. Eleven babies did not have UTS data and 24 mothers could not be included as they were matched to the six cases without UTS data. Therefore there were 708 mother–infant dyads (729 babies) in the control group. There was a larger proportion of missing 'case' babies (21/193) than controls (39/752): $\chi^2=8.38$, $P=0.004$, RR=2.09, CI 1.26–3.48. This was not because there was any difference in the proportion of cases leaving the practice compared with controls ($\chi^2=1.41$, $P=0.24$). Of the 21 cases in which the baby was unidentified, 7 of the mothers had a diagnosis of schizophrenia, 3 of bipolar disorder, 3 of paranoid psychosis, 1 of schizo-affective disorder and 1 of puerperal

psychosis; in 6 the diagnosis was not known. Of the 39 control participants with unidentified babies, 1 had a diagnosis of drug dependence and 5 had depression. Seven case and six control questionnaires were returned which revealed that, of the 20 cases without linked baby data, three babies were looked after by social services and one control-group baby had been adopted.

There was no significant difference in follow-up times for babies in either group (cases, median 366, range 31–366; controls, median 366, range 30–366; Kruskal–Wallis test, $P=0.36$).

There was one death attributed to sudden infant death syndrome (SIDS) in a case baby but no infant death in the control group (Fisher's exact test, $P=0.04$). The mother of this baby had had a diagnosis of 'psychosis NOS' several years before the date of delivery.

There was no significant difference in the rate of accidents (RR=0.98, 95% CI 0.55–1.74, $z=-0.07$, $P=0.9$), hospital referrals (RR=1.31, 95% CI 0.89–1.94, $z=1.37$, $P=0.17$), contact with accident and emergency departments (RR=1.12, 95% CI 0.58–2.16, $z=0.33$, $P=0.74$) or hospital admissions (RR=0.83, 95% CI 0.47–1.47, $z=-0.635$, $P=0.53$) between cases and controls. There was also no significant difference in the rate of one or more immunisations ($z=-0.72$, $P=0.47$) or in the rate of first immunisation ($z=-0.65$, $P=0.52$) in the first 3 months of life. However, in the period 90–270 days after birth, babies in the case group were less likely to have had one or more immunisations (RR=0.94, 95% CI 0.88–0.99, $P=0.03$) and there was a trend for babies in this group to have their first immunisation during this period (RR=1.9, 95% CI 0.81–4.34, $P=0.15$). When this analysis was limited to mothers with active illness during or after pregnancy (any appointment during or before pregnancy, or any admission during pregnancy or taking any

psychiatric medication after pregnancy) there was no significant change in any of the above rates.

DISCUSSION

Main findings

There was no difference in gestational age at antenatal booking for mothers with a history of psychotic disorders and matched general practice controls. We used gestational age at booking as a proxy for attendance for antenatal care. Some authors have suggested that women with mental illness are less likely to attend antenatal clinics (Bagedahl-Strindlund, 1986; Goodman & Emory, 1992), but this may be due to a failure to control for social class and neighbourhood, which we have tried to do by matching for general practice. The different nature of health care services in different countries may also explain this difference in findings, as the UK National Health Service aims to provide integrated care through primary care.

We found that general practitioners were less likely to record alcohol intake or smoking status during pregnancy or to give contraceptive advice post-partum to women in the case group compared with controls. This suggests that routine but important aspects of antenatal care such as alcohol consumption, smoking and physical health problems (as we found with the lower prescribing of anti-asthmatic drugs in cases) may be neglected, possibly because general practitioners may tend to focus on the psychotic illness of their patients.

Women designated as cases were significantly more at risk of stillbirths and neonatal deaths in this study, unlike the large study using case registers by Bennedsen et al (2001), which did not find an increased incidence of stillbirths in women with schizophrenia. There have been few studies of the incidence of stillbirths and neonatal deaths for women with psychotic disorders in recent years, when obstetric care has improved. Our finding may be due to these patients' lifestyles (e.g. smoking, substance misuse) and pharmacological treatment during pregnancy, although the latter did not explain our result when entered into a logistic regression. Data on medication prescribed in secondary care may not be fully recorded on a primary care database, particularly the atypical antipsychotic drugs prescribed in 1996–1998, so there may be

Table 1 Stillbirths, neonatal deaths and infant deaths in children of women with a psychotic disorder ($n=199$) compared with a control group ($n=787$)

	Cases n (%)	Controls n (%)	OR (95% CI)	P
Stillbirths	5 (2.5)	5 (<1)	4.03 (1.14–4.25)	0.03
Neonatal deaths	4 (2)	0		<0.001[1]
Infant deaths	1 (<1)	0		0.04[1]

1. Fisher's exact test.

residual confounding. Data on smoking and substance misuse were not recorded adequately on the GPRD and could therefore not be analysed as a potential predictor.

There was one report of SIDS in a case baby (*P*=0.04) whose mother had a diagnosis of psychosis NOS. We cannot draw conclusions on the basis of one such case, although it is of note that Bennedsen *et al* (2001) reported an increased risk of SIDS for women with schizophrenia. These authors suggested that this might be due to an inadequate reaction by these mothers if their children become ill, leading to insufficient medical treatment. However, we found no significant differences in the rates of all types of hospital contact in case and control babies during the first year of life.

The case babies in the care of their biological families were taken for immunisations later than those in the control group, but they did not have an increased risk of medical problems in the first year of life, as measured by hospital contacts. This may be due to increased surveillance from health visitors or reflect support from the family; alternatively, the study might have lacked the statistical power to show any differences. Nevertheless, this study does suggest that the babies are medically well and therefore adequately cared for by the mother and her social network. However, this study could not examine other important aspects of care for the infant such as emotional responsiveness, which may be impaired (Riordan *et al*, 1999).

Methodological limitations

Methodological limitations of this study include potential bias from patients lost to follow-up and from misclassification. Loss to follow-up should be minimal, as registrations with general practices and exits from the database are carefully recorded. However, a higher proportion of case babies were unidentified compared with controls and, where more was known about these unidentified babies, more from the case group were looked after by social services. This study can therefore provide results only on babies who remained with their biological mothers and where both baby and mother were registered with the same general practitioner.

Misclassification of diagnosis is possible, but a study of diagnoses of psychosis using this database has demonstrated high predictive values (Nazareth *et al*, 1993).

The proportions of diagnostic categories of psychosis found in all women of child-bearing age on the GPRD, from which these pregnant women have been identified (Howard *et al*, 2002), were similar to those for an epidemiologically representative population of patients with psychosis identified in south London (Thornicroft *et al*, 1998). The prevalence of schizophrenia on the GPRD was 29.2 per 10 000 in 1996 and 30 per 10 000 in 1997, which is similar to previous estimates of incidence and prevalence in the UK (Meltzer *et al*, 1995; Macfarlane *et al*, 2000). Nevertheless, there is a trade-off between using a large, nationally representative primary care database, which can provide important data from a large sample, compared with studies involving detailed clinical information with more direct clinical applicability. Specific diagnostic categories found on the GPRD are therefore unlikely to be exactly the same as those found in research and psychiatric practice but can be grouped together for broad diagnostic syndromes which are likely to have similar management.

Obstetric data on the GPRD appears comparable with national statistics: 14% of the participants in our control group had had Caesarean sections and 9% had had instrumental deliveries, which is comparable with the proportion in England in 1994–1995 (15.5% and 10.6% respectively; Macfarlane *et al*, 2000). Similarly, we found 6.4 stillbirths per 1000 total births in our control group, which is comparable with 5.4 stillbirths per 1000 total births in 1996 in England and Wales (Macfarlane *et al*, 2000).

We could not investigate the effect of socio-economic status in this study – we matched controls for general practice, which is a proxy for neighbourhood, although there is some debate as to how accurately neighbourhood can act as a proxy for socio-economic status (McLoone & Ellaway, 1999). Matching for general practice (and social class) means that social class cannot be investigated further in this study. Although social class also influences health-seeking behaviour (Department of Health and Social Security, 1980), the outcomes presented here are of major episodes of infant medical problems, which are less likely to be influenced by socio-economic status.

This study involves large numbers of women, but the sample size is not large enough to detect subtle differences in the rates of individual medical conditions because many of the outcomes of interest are relatively rare. Nevertheless, any substantial differences in risk that are detected are of major importance to mothers with psychotic disorders and it is these that are potentially amenable to interventions. The fertility of women with psychotic disorders was found to be considerably lower than that of matched controls on the GPRD between 1996 and 1998 (Howard *et al*, 2002), and patients who were found to have delivered babies in that study were used for the case cohort here. The low fertility of patients with psychotic disorders also means that it is difficult for any service to cater specifically for these vulnerable women and their families when there are few in any specific catchment area.

Clinical implications

Despite changes in obstetric care over the past few decades, the increased risk of stillbirths and neonatal deaths for women with a history of psychotic disorders found here is consistent with early studies. It is therefore essential for primary and secondary health care professionals to focus on optimal obstetric care and ensure good liaison between health professionals, particularly in view of the poor smoking and alcohol histories found recorded in primary care here. We know that a small proportion of women with a psychotic disorder have significant parenting difficulties. However, this study suggests that the physical health of babies living with their biological mothers who have a psychotic disorder is not significantly different from that of matched baby controls in an epidemiologically representative population. This might remove some of the stigma these mothers have to face. Future research should investigate patients' perceptions of their health and social care needs during and following pregnancy.

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CLINICAL IMPLICATIONS

■ This study provides further evidence that the babies of women with psychotic disorders are at increased risk of stillbirth and neonatal death and that the mothers therefore need optimal antenatal care, including advice on smoking and substance misuse.

■ Good liaison between primary care, psychiatric and obstetric health professionals is essential in the care of pregnant women with psychotic disorders.

■ Infants of mothers with psychotic disorders who remain with their biological families do not have an increased risk of accidents or other medical problems in the first year of life, and maternal diagnosis of psychosis alone does not therefore lead to poor medical outcome.

LIMITATIONS

■ Diagnoses of psychotic disorders were clinical diagnoses recorded by general practitioners, and misclassification is therefore possible.

■ Some mother–infant dyads were lost to follow-up and this might have led to selection bias.

■ The sample size, although large, may be too small to detect subtle differences in the rates of individual medical conditions, as many of the outcomes of interest are relatively rare.

LOUISE M. HOWARD, MRCPsych, Institute of Psychiatry, London, UK; CLAUDIA GOSS, MD, Section of Psychiatry, University of Verona, Italy; MORVEN LEESE, PhD, GRAHAM THORNICROFT, FRCPsych, Institute of Psychiatry, London, UK

Correspondence: Dr Louise M. Howard, Health Services Research Department, Box PO29, Institute of Psychiatry, London SE5 8AF, UK. Tel: 020 7848 0735; fax: 020 7277 1462; e-mail: l.howard@iop.kcl.ac.uk