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Obstetric Complications and Schizophrenia
A Case–Control Study

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Schizophrenics have been repeatedly found to experience more obstetric complications (OCs) at birth. The meaning of such a finding is debated, and the aim of this study is to contribute to the understanding of OCs' aetiological role in schizophrenia. We compared a group of schizophrenic patients with their siblings and controls, on the basis of obstetric files stemming from the same University Hospital Maternity Ward. Schizophrenic patients had more frequent umbilical cord complications and atypical presentations, as well as higher scores on a scale measuring OCs linked to possible neonatal asphyxia.

Schizophrenia is considered by most clinicians and researchers as an epigenetic developmental process. This concept, dating back to the beginning of the century (Bleuler & Jung, 1908), states that some inherited and/or early environmental factors could lead to a neurodevelopmental defect (Weinberger, 1986; Murray & Lewis, 1987; Cannon *et al*, 1989; Lewis, 1989; Mednick *et al*, 1989), favouring the constitution of a vulnerability to schizophrenia (Meehl, 1962, 1989; Zubin, 1986; Nuechterlein, 1987). Among early non-genetic factors, interest has focused on infectious (Barr *et al*, 1990; O'Callaghan *et al*, 1991) and perinatal complications.

Since the pioneer publications by Pasamanick and his colleagues (Pasamanick *et al*, 1956; Pasamanick & Knobloch, 1960), a number of epidemiological studies have evaluated obstetric complications (OCs) as a potential co-factor for schizophrenia (for review see McNeil & Kaij, 1978; McNeil, 1987). Methodological difficulties have been identified in the majority of the studies (Lewis *et al*, 1989; Eagles *et al*, 1990). Using a prospective design, Done *et al* (1991) did not find any association between OCs and schizophrenia. However, they assumed that the nature of the relevant OCs for the later development of schizophrenia should be "the same as those responsible for stillbirth and neonatal death", a hypothesis which has been questioned (Kerwin & Woodhouse, 1991; O'Callaghan *et al*, 1992). The recent study by O'Callaghan *et al* (1992) supports the hypothesis of an association between OCs and schizophrenia; on the basis of their results, they suggest that OCs may be secondary to yet earlier events. Thus, the co-occurrence of OCs and schizophrenia is well established, but its meaning is still debated. Some authors postulate that OCs act in synergy with the genetic loading (diathesis–stress model; Parnas, 1990), whereas others find them to be more frequent in 'non-familial' schizophrenics only (Lewis & Murray, 1987; O'Callaghan *et al*, 1990*a*), a finding which has been contradicted by DeLisi *et al* (1988), Nimgaonkar *et al* (1988), and O'Callaghan *et al* (1992). Most authors agree that OCs are often associated with increased ventricule: brain ratio (VBR) (Reveley *et al*, 1984; Pearlson *et al*, 1985; Turner *et al*, 1986; Lewis & Murray, 1987; Murray *et al*, 1988; Owen *et al*, 1988; Silverton *et al*, 1988). An association of OCs with an earlier onset of schizophrenia and/or a poorer outcome has also been reported (Wilcox & Nashrallah, 1987*a*,*b*; Parnas, 1990; O'Callaghan *et al*, 1992).

The purpose of this study was to examine the frequency and the nature of OCs in schizophrenics, comparing both to their siblings and to a control group from the general population. Some methodological issues are also addressed.

Method

The study relies on the obstetric files of 42 schizophrenics and 40 of their siblings, stemming from 41 mothers, and of 174 controls, stemming from 92 mothers; thus 256 subjects (142 males and 114 females) born between 1925 and 1971 (median 1951). This sample is derived from a larger one, described elsewhere (Bovet, 1990), in which schizophrenics admitted in the University of Lausanne Psychiatric Clinic between 1 January 1980 and 30 April 1986 had been considered. For every sampled patient, a control had been drawn from the Birth Register of Lausanne, matched by sex and date of birth. Both patients and controls had to be of Swiss nationality, as for every Swiss citizen and his/her family members in the paternal lineage, name, forenames, birth and death are registered in a place defined as the family's 'place of origin', wherever the actual places of birth or death may have been. Thus, these civic state registers had allowed the sampling of all siblings of both patients and controls.

Table 1
OCs appearing most frequently: weight in the different scales, and frequency

Complication	Pregnancy	Delivery	Risk of asphyxia	% ($n = 354$)
Acute foetal distress	0	3	1	17.8
Atypical presentation	0	2	0	4.8
Birth weight 1500-2500 g	0	2	0	5.1
Blood group incompatibility	2	0	0	4.8
Contracted pelvis	0	0	1	12.1
Delivery 32-37 weeks	2	0	2	5.6
Illness, accident, drugs during pregnancy	2	0	0	9.9
Inhalant analgesia during labour	0	3	1	46.6
Instrumental delivery: forceps	0	3	3	6.2
Labour 12-24 hours	0	2	0	20.9
Nausea, vomiting during pregnancy	1	0	0	12.1
Newborn cyanosis	0	0	3	5.1
Pathological placenta	0	0	1	4.2
Perineal trauma	0	1	0	30.2
Post-partum haemorrhage	0	2	0	10.5
Pre-eclampsia (moderate or severe)	2	0	0	9.0
Umbilical cord: encircling	0	2	2	23.7

From the original sample, we considered those who were born in the Maternity Ward of the University Hospital (of course, with this procedure, the original matching by sex and date of birth was lost). Four were eliminated because their files were missing, and 11 because they died before the age of 17.

The original sample also contained non-psychotic in-patients admitted in the same period, matched with schizophrenics by sex and year of birth, and their siblings. This group was not specifically studied, because it lacked clinical homogeneity and was of a lower social status. However, its data were retained when we checked the effects of sociodemographic variables on OCs, in order to increase the total number of subjects ($n = 354$) and maximise the probability of detecting such effects.

The diagnosis of schizophrenia was made according to the Bleulerian Criteria (Bleuler, E., 1911; Bleuler, M., 1972) as they had been used in the Lausanne inquiry (Ciompi & Müller, 1976; Ciompi, 1980). Psychiatric files of each patient were re-examined by using Research Diagnostic Criteria (Spitzer *et al*, 1978): 38 schizophrenics fitted completely, 4 partially.

The obstetric files were found in the archives of the maternity ward, and were examined without knowledge of the adult psychiatric outcome. These files had been filled in by obstetricians, and not by midwives, which accounts for their detailed and accurate content. The relevant data were summarised in 44 items, describing pregnancy and perinatal evolution. One of us (PH) created two weighted scales for pregnancy and delivery complications. In an attempt to isolate items linked to neonatal asphyxia, one more scale, focusing on risks of asphyxia, was created. The most frequent items and their weighting are described in Table 1. Moreover, we scored the subjects on the Obstetric Complications Scale developed by Lewis *et al* (1989), which was proposed for studies based on maternal recall or psychiatric charts. This scale scores the presence of at least one 'definite' complication (score 2), or of at least one 'equivocal' complication (score 1).

Firstly, the effects of seven sociodemographic variables on OCs were studied, using χ^2 or Kruskal–Wallis tests. These variables are: sex, birth order, month of birth, year of birth, father's profession, and mother's and father's age at subject's birth. In the whole sample of 354 subjects (schizophrenics and their siblings, controls of the general population, and non-psychotic hospitalised patients), these variables were studied one by one on the separate OC items which were present in more than 10 subjects. Continuous variables (year of birth, mother's and father's age) have been transformed into categorical ones.

Secondly, OCs occurring in more than five subjects (i.e. 29 items) were compared between three subsamples: schizophrenics, their siblings, and children drawn from the general population. We compared the occurrence of the items by 2×2 comparisons, using χ^2 or Fisher's exact probability tests. Scores on the weighted scales were compared using either Mann–Whitney or Kruskal–Wallis tests. Scores on Lewis *et al*'s scale were compared through χ^2 test. Birth weight and skull dimensions were compared through a parametric test (analysis of variance). Results were considered significant if $P < 0.05$; nevertheless, we mention differences reaching $P < 0.10$ as indications for possible future studies.

Results

Three sociodemographic variables were found to be statistically related to OCs: sex, month of birth, and birth order. The use of forceps and the resuscitation of the newborn are more frequent in males ($P < 0.05$), and threatened abortion in females ($P < 0.05$). The number of OCs is not evenly distributed between the various months of birth (Kruskal–Wallis, d.f. = 11, $P < 0.01$); however, the months with more OCs are not consecutive ones, but scattered throughout the year. Birth order is significantly related to eight different items: prolonged labour, premature rupture of membranes, chorioamnionitis, forceps

delivery, acute foetal distress, uterine contractions insufficiency, and respiratory distress syndrome, which are more frequent among only and first-born children. Pathological placenta is absent among the latter, and found mainly in last-born children. There are no significant relationships between OCs and fathers' profession, nor between OCs and either mothers' or fathers' age. The distribution in the subsamples of these three demographic variables is as follows: month of birth and sex are evenly distributed, whereas birth order is not. Only children are overrepresented in the schizophrenic group, and by definition absent from the siblings group.

Obstetric techniques have changed between 1925 and 1971, leading to a generation effect. We divided the sample into three periods of birth: before, during, and after the ten post-war years, in which major changes in obstetric procedures occurred. For example, labour longer than 12 hours is found in one out of three deliveries before 1950, as compared to one out of eight after 1950; cyanosis of the newborn is registered only since 1950, rhesus incompatibility since 1954. This generation effect has to be taken into account when comparing schizophrenics with their siblings, because among the latter are children born in more recent years, who just entered the risk period for schizophrenia when we drew the sample.

Schizophrenics v. siblings and controls

When comparing the occurrence of OCs between the groups, three specific complications are found more frequently in schizophrenics. A significant difference appears for umbilical cord encircling and knot (16 schizophrenics out of 42; 5 siblings out of 40; 38 controls out of 174), and for atypical foetal presentation (five, one and six cases respectively). Odds ratio is 2.20 for umbilical cord complications, and 3.78 for atypical presentation. Labour over 24 hours is more frequent in schizophrenics than in their siblings, but the difference does not reach statistical significance. No other significant differences are found on singular items. Umbilical cord complications and atypical foetal presentation are not influenced by birth order, nor by generation effect, whereas prolonged labour is influenced by both.

We found no significant differences concerning birth weight, birth size or skull dimensions.

As far as scales are concerned, no significant differences were found on the scale of pregnancy complications, nor on that of delivery complications. On the scale of risks of asphyxia, scores were higher for schizophrenics (2.9), compared to both their siblings (1.8) and the controls (2.2). The difference only reaches statistical significance between schizophrenics and their siblings. Even when the influence of umbilical cord complications is eliminated, scores remain higher for schizophrenics, but the difference is no longer significant. The influence of birth order is particularly strong on this scale, and the influence of generation effect can hardly be controlled.

On Lewis *et al*'s (1989) scale, the difference is significant between schizophrenics and their siblings ($P<0.05$), as well as between schizophrenics and controls ($P<0.01$). Definite complications are found in 19 schizophrenics, 12 of their siblings, and 57 controls. Birth order influence on this scale is marked ($P<0.06$). No influence of sex was detected.

Discussion

In the studies on OCs and schizophrenia, some methodological aspects have to be pointed out. First, the sampling procedure, which varies considerably between researchers. Some researchers sampled schizophrenics with a chronic evolution (O'Callaghan *et al*, 1990*a*), others familial cases of schizophrenia (DeLisi *et al*, 1988), or high risk children (Parnas *et al*, 1982). Our sampling of hospitalised schizophrenics leads to a slight selection bias toward chronicity. But it has to be remembered that, using the Bleulerian diagnostic criteria, the long-term outcomes in more than half of the hospitalised schizophrenics is favourable (Ciompi, 1988). Thus, we feel our selection bias is not very important. In fact, the only way of avoiding selection bias would be a community study, which is hindered by the low morbid risk for schizophrenia.

The second methodological point is the source of the OCs data. Only a minority of researchers relied on sources which had not been retrospectively influenced by the outcome of the subjects, such as obstetric files or midwife protocols. Most studies are based on mothers' reports and/or psychiatric charts, which are probably biased sources, even though O'Callaghan *et al* (1990*b*) claim that maternal recall is reliable. Our findings using Lewis *et al*'s scale can throw some light on that claim. Whereas Lewis and colleagues (Lewis & Murray, 1987; Lewis *et al*, 1989) found 'definite' complications in 17% of schizophrenics and in 8% of controls, our rates were 45% and 32%, respectively, which suggests a low sensitivity of maternal recall. Lewis & Murray (1987) already pointed out that errors in maternal recall are of omission rather than commission. Even in studies relying on obstetric records, little attention was paid to changes in obstetric procedures and techniques over a long period of time. Our findings, relying on obstetric files stemming from the same University Ward, show that generation effect should be taken into consideration.

In a similar way, the sex of the newborn and its birth order have to be taken into account, as they were shown in this study to influence OCs. As far as month of birth is concerned, our finding of increased OCs in some isolated months is, in our opinion, of little if any importance, as it cannot be related to any psychiatric or obstetric hypothesis. The effect of demographic variables is particularly difficult to evaluate in findings relying on scales, in which items divergently influenced by these variables are pooled.

The general finding emerging from studies on OCs and schizophrenia is that schizophrenics are more likely to have a history of OCs than are non-schizophrenic controls (Lewis *et al*, 1989). Authors disagree on the possible interactions between OCs and other aetiological co-factors, mainly the genetic one. However, the hypothesis drawn from this finding can be roughly summarised as follows. OCs could lead to a neonatal asphyxia, which in turn might lead to some cerebral defect favouring the future development of the disease. Our finding of a significant increase on the scale of risk of asphyxia may be an argument supporting such a hypothesis. However, we want to point out that the scale 'risk of asphyxia' is made up of items which *may* lead to a neonatal asphyxia, but are not always associated with a *real* asphyxia. For example, to be born with the cord around the neck may be a cause of asphyxia, but is actually considered as a benign and frequent complication, occurring in 20% of all deliveries (Spellacy *et al*, 1966). Unfortunately, data collected on deliveries occurring prior to 1970 cannot provide reliable measurements of the actual degree of asphyxia. No increase was found on our scales of pregnancy and delivery complications. Thus, these findings allow us to confirm the increase of OCs described in the other studies, as far as OCs leading to a possible neonatal asphyxia are concerned.

When considering specific items, we found two OCs to be significantly more frequent in schizophrenics: cord encircling and knot, and atypical presentation. Since 29 items were studied, the risk of a chance finding cannot be excluded. But it has to be pointed out that atypical presentation and, to a lesser degree, umbilical cord complications were also more frequent in the Danish high-risk sample (Parnas *et al*, 1982). For prolonged labour, our finding is more dubious, whereas others found it clearly increased (Jacobsen & Kinney, 1980; Wilcox & Nasrallah, 1987*a*,*b*). We want to stress that no differences appear in the skull dimensions of the newborn. This result is particularly interesting in the light of the controversial finding of a reduced head circumference in adult schizophrenics (Andreasen *et al*, 1986, 1987; DeLisi & Goldin, 1987; Reveley & Reveley, 1987; Stevens & Waldmon, 1987; Weinberger *et al*, 1987; Jones & Lewis, 1991).

Our attention has been drawn to the nature of the two single complications which were found to be increased. At the end of the intrauterine life, to prepare oneself for a favourable delivery, that is with a good presentation and without the cord encircling, requires from the foetus a fine perceptual and motor adjustment to its rapidly changing environment. These two OCs cannot be accounted for by smaller mothers' pelvises, nor by schizophrenics' birth weight, size or head circumference, as we found no differences on these items. Thus, we propose to consider the following bold hypothesis: these two complications might be related to a sort of '*in utero* clumsiness' of the foetus, reflecting a previous neurodevelopmental impairment (Lyon *et al*, 1989; Blennow & McNeil, 1991). The hypothesis that OCs may be the consequence of pre-existent foetal abnormalities has already been formulated by others (Shields & Gottesman, 1977; Goodman, 1988*a*,*b*; O'Callaghan *et al*, 1992).

In conclusion, our study is in accordance with most of the findings reported in the literature: we find a co-occurrence of schizophrenia and OCs. However: (a) the exact nature of the OCs is still debatable; and (b) the one-way causal hypothesis considering OCs as a possible aetiological factor should be questioned. OCs could also be the consequence of a pre-natal neuronal disorder. This does not rule out the possibility that OCs enhance the risk of a neonatal asphyxia and of some brain injury, which in turn could favour ventricular enlargement and the development of a deficitary form of schizophrenia. In that hypothesis, neonatal asphyxia would be a risk factor for the prognosis of the disease, and not for its incidence.

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