Obstetric complications and clinical presentation in first episode of psychosis

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Abstract

Objective: Psychotic disorders exhibit a complex aetiology that combines genetic and environmental factors. Among the latter, obstetric complications (OCs) have been widely studied as risk factors, but it is not yet well understood how OCs relate to the heterogeneous presentations of psychotic disorders. We assessed the clinical phenotypes of individuals with a first episode of psychosis (FEP) in relation to the presence of OCs. Methods: Two-hundred seventy-seven patients with an FEP were assessed for OCs using the Lewis–Murray scale, with data stratified into three subscales depending on the timing and the characteristics of the obstetric event, namely: complications of pregnancy, abnormal foetal growth and development and difficulties in delivery. We also considered other two groups: any complications during the pregnancy period and all OCs taken altogether. Patients were clinically evaluated with the Positive and Negative Syndrome Scale for schizophrenia. Results: Total OCs and difficulties in delivery were related to more severe psychopathology, and this remained significant after co-variating for age, sex, traumatic experiences, antipsychotic dosage and cannabis use. Conclusions: Our results highlight the relevance of OCs for the clinical presentation of psychosis. Describing the timing of the OCs is essential in understanding the heterogeneity of the clinical presentation.

Significant outcomes

- OCs are associated with more severe psychopathology.
- Difficulties during delivery are specifically associated with worse psychopathology.
- OCs are heterogeneous, and timing description is essential.

Limitations

- The OCs included come from a clinical scale, so some others may be missing.
- OCs were not analysed individually but as groups according to specific characteristics.
- OCs were recorded through a familiar interview.
Introduction

First episode of psychosis (FEP) can be the initial event of a wide variety of diagnoses and eventually lead to schizophrenia, bipolar disorder, major depression disorder and other clinical entities (Salvatore et al., 2009). Regardless of diagnostic heterogeneity, genetic and environmental factors interact with the risk pathway. Among the environmental factors, obstetric complications (OCs) or abnormalities during the prenatal and perinatal period have historically been described as major risk contributors (Cannon et al., 2002; Davies et al., 2020). However, current evidence suggests that OCs in psychosis are a risk factor not only for the later development of psychosis but also for other effects that range from neuroanatomical (Costas-Carrera et al., 2020), neurocognitive (Amoretti et al., 2022), metabolic abnormalities (García-Rizo et al., 2015) to clinical psychopathology (Mezquida et al., 2021). Moreover, some specific clinical features, such as childhood attention deficit hyperactivity disorder symptoms in schizophrenia-spectrum disorders, seem to be associated with OCs (Peralta et al., 2011), while higher ratings of parkinsonism, catatonia and dyskinesia have been associated with OCs in neuroleptic-naïve psychotic patients (Peralta et al., 2006; Peralta & Cuesta, 2010). However, there remains much inconsistency between studies on how OCs are measured, as some authors include OCs as a discrete entity while others specify the timing and the nature of the obstetric event (Mezquida et al., 2018).

The perinatal origins of psychosis model are receiving increasing attention (García-Rizo & Bitanhirwe, 2020), particularly within the realm of metabolism (i.e. logic and theory). This field of enquiry in general medicine originated as the “Barker hypothesis”, where the relationship between foetal growth and later type 2 diabetes mellitus (T2DM) (Hales & Barker, 1992) established a theoretical basis for the developmental origins of health and disease model (Gluckman & Hanson, 2006). This model suggests that “undesirable conditions” during the perinatal period can have long-lasting metabolic consequences. Indeed, recent research showed that birth weight (BW), an indirect measure of the intrauterine milieu, is related to weight gain (García-Rizo et al., 2020; Garriga et al., 2019a) and glucose values in FEP (García-Rizo et al., 2022), with T2DM in schizophrenia (Fernandez-Egea et al., 2020) and in affective disorders (Garriga et al., 2019b).

However, the study of OCs and their relationship with clinical presentation in psychiatric patients has received less attention. OCs taken as a whole were associated with more prominent negative symptoms in patients with chronic schizophrenia and early onset in adolescence (Kotlika-Antczak et al., 2001). OCs were associated with negative symptoms in less affluent patients with schizophrenia (Jones et al., 2011). Similar outcomes were observed in an African cohort, where OCs were associated with negative symptomatology (Mechri et al., 2008). Interestingly negative symptoms were also associated with OCs in the adolescent with psychotic-like experiences (Cardno et al., 2021), while also in adolescents, adverse events during early development (both prenatal and perinatal) lead to an increased risk of developing non-clinical psychosis-like symptoms (Zammit et al., 2009).

When specifically evaluating the type of OCs, previously published work by Kotlika-Antczak and colleagues has described more prominent negative symptomatology to be associated with abnormalities in delivery evaluated with the Apgar score (Kotlika-Antczak et al., 2001) while a recent cross-sectional study in patients with chronic schizophrenia with predominant negative symptomatology described an association between difficulties during delivery assessed with the Lewis–Murray scale and measures of anxiety, guilt feelings and unusual thought content (Mezquida et al., 2021).

BW, an indirect marker of the prenatal environment, has been studied in a Finnish schizophrenia study sample, where both low and high BW were associated with more severe symptoms, especially in terms of “bizarre” behaviour, affective flattening and attentional impairment (Wegelius et al., 2013). In addition, the same study found low BW to be associated with more severe formal thought disorder (Wegelius et al., 2013). However, another study stratifying the study cohort into deficit and non-deficit schizophrenia did not find any association with low BW (Alabaf et al., 2022). Maternal smoking, an indirect marker of an adverse intrauterine environment, has been correlated with lower BW (Abraham et al., 2017) and also with negative symptomatology (Stathopoulou et al., 2013). Indeed, a later study found that maternal smoking was associated with more severe deficit symptoms (Bernardini et al., 2015). Additionally, recent research evaluating the effect of maternal cortisol during pregnancy highlights the importance not only of timing but also of foetal sex (Ellman et al., 2019). Indeed, in a large schizophrenia hospital cohort, OCs were associated with negative symptomatology only in females (Gallagher et al., 2014).

Nevertheless, negative findings have also been described. No association was described between OCs and clinical psychopathology neither in a Nigerian cohort of patients diagnosed with schizophrenia (Onu & Ohaeri, 2020) nor in a cohort of severely ill schizophrenia patients (Smith et al., 1995).

OCs have been related to clinical symptomatology not only in schizophrenia but also in affective disorders (Serati et al., 2020; Solé et al., 2020; Sagué-Vilavella et al., 2022). In a longitudinal study, hypomania with previous psychotic experiences was initially associated with gestational influenza; however, later analysis did not confirm the association (Anderson et al., 2016). Nevertheless, in the general population, a study evaluating a wide range of psychopathology measures in offspring suggested that the association between prenatal and postnatal factors and psychopathology of offspring during adulthood was mediated by familial factors (Essau et al., 2018). Beyond this, recent research focussing on FEP highlights the effect of other environmental factors in later life related to psychopathological profile at onset of psychiatric illness, such as childhood adversity (Butjosa et al., 2022) and cannabis use (González-Blanco et al., 2021; Safont et al., 2022).

Built on the rationale described above, in this paper, we aimed to evaluate the clinical presentation and characteristics of a cohort of FEP according to their profile of OCs.

Material and methods

Study setting

This study is part of the multicentre Project ‘Phenotype–genotype interaction: application of a predictive model in first psychotic episodes’, the PEPs study, which is a longitudinal cohort study examining gene–environment (GxE) interactions on the pathway to psychosis. A complete description of the PEPs protocol has been published previously (Bernardo et al., 2019, 2013).

The PEPs Project incorporates clinical parameters from various assessments/visits: baseline, 2-month, 6-month, 1-year and 2-year follow-up. For the present study, we have focussed on baseline visits.
**Subjects**

Three-hundred thirty-five FEP patients were included in the PEPs Project, running between 2009 and 2011 at 16 Spanish hospitals that participated in the Biomedical Research Networking Center for Mental Health (CIBERSAM) (Salagre et al., 2019), which is following up a cohort of patients with FEP (Fraguas & Díaz-Caneja, 2021). From those 335 patients recruited initially, due to missing data required for the analyses, only 277 were included in the study.

Patients were included if they met the following inclusion criteria: aged between 7 and 35 years old at recruitment; presence of psychotic symptoms of less than 12-month duration; the ability to speak Spanish correctly and providing written informed consent. The exclusion criteria were an Intelligent Quotient (IQ) lower than 70 and with significant difficulties or malfunctioning with adaptive processes, history of head trauma with loss of consciousness and the presence of an organic disease. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and adhered to Good Clinical Practice guidelines. Ethics committees of all participating centres approved the current study. As inclusion criteria, informed consent was obtained from all participants or from parents or legal guardians of under-age subjects.

**Antipsychotic treatment**

As most of the participating centers were tertiary university hospitals, a large majority of the patients included in the study were recruited during their first hospitalisation, when the first anti-psychotic treatment was initiated. In the whole sample recruited, the majority of the patients ($n = 304, 90.7\%$) were taking antipsychotic treatment by the time they were included in the study, with a mean 54.08 days of treatment (Biongue et al., 2016). Only a small proportion ($n = 49, 14.6\%$ of the sample) had been taking antipsychotic for more than 3 months before the inclusion. A previous report gave a full description of the psychopharmacological treatment used in this study (Biongue et al., 2016). The prescribed daily dose (PDD) for a drug was defined as the daily dose of a drug formulation, oral or injectable, calculated separately for each treatment day of an individual patient who was treated with this drug formulation for at least three consecutive days (irrespective of the dose). To compare the different antipsychotics, the PDDs doses of antipsychotics were converted to an estimated daily equivalent doses of chlorpromazine (CPZ) following the international consensus (Gardner et al., 2010).

**Clinical assessments**

At baseline, a complete psychiatric personal and family history was performed in a systematic interview, including OCs registration, substance use and traumatic experiences.

Clinical symptomatology was assessed using the Spanish-validated version of the Positive and Negative Syndrome Scale for Schizophrenia (PANSS) (Peralta & Cuesta, 1994), a semi-structured interview with 30 items rated on a seven-point scale.

Drug use was evaluated by a part of the European Adaptation of a Multidimensional Assessment Instrument for Drug and Alcohol Dependence (EuroPasi) (Kokkevi & Hartgers, 1995). In the inclusion visit, a systematic register of drug misuse habits was performed. For the present study, we focussed on cannabis consumption, and we registered its use as dichotomous exposure or no exposure. The number of traumatic experiences was collected from the list of events that appear in the Traumatic Experiences in Psychiatric Outpatients Questionary (TQ) (Davidson & Smith, 1990). This tool is an 18-item self-reported questionnaire that assesses the presence of stressful events across the lifespan. As Mas et al. (2020) highlighted, due to the high heterogeneity of traumatic experiences on the item list, we only recorded the total number of experiences. These data were encoded and registered as ‘No exposure’ (non-traumatic experiences during childhood) and ‘Any exposure’ (one or more traumatic experiences during childhood) (Vassos et al., 2019; Mas et al., 2020).

**Obstetric complications**

OCs were assessed using the Lewis–Murray scale through familiar interviews (Lewis et al., 1989). This approach has proved accurate in previous samples (Borroja et al., 2011). The Lewis–Murray scale allows describing adverse events as absent, equivocal or definite. We only included definite scores as present ones. The scale also groups OCs into three categories, A, B and C (Cannon et al., 2002; Mezquida et al., 2018) according to the type of complication defined as follows:

A. Complications of pregnancy (syphilis or rubella, rhesus isoimmunisation/Rh incompatibility, severe preeclampsia, requiring hospitalisation or induction of labour and bleeding before delivery of threatened abortion);

B. Abnormal foetal growth and development (twin delivery, preterm birth week less than 37 weeks or long-term birth week of more than 42 weeks, weight at birth less than 2500 g and any important physical abnormality);

C. Difficulties in delivery (including premature rupture of membranes, duration of delivery more than 36 h or less than 3 h, umbilical cord prolapse, complicated caesarean delivery, abnormal foetal presentation, use of forceps and being in an incubator for more than 4 weeks).

**Statistical analysis**

Socio-demographic and other descriptive variables were assessed through univariate analyses. As for OCs, both the total numbers as well as their subtypes (A, B and C) were considered as dichotomous variables (yes/no). The Total-T group comprehended all the OCs. Particularly, as we were interested in evaluating the effect of OCs according to their timing of appearance, we created another group for analysis purposes, viz., any OC during gestation AB (from the combination of groups A and B).

To assess differences among patients with or without OCs in terms of psychopathology, independent t-test analyses of the PANSS and its subscales between the groups studied (OCs and their subtypes) were performed. Then, analyses of covariance (one-way ANCOVA) were performed to remove possible confounding factors in the association between OCs and psychopathology. In the model, PANSS subscales (positive, negative or general psychopathology) or total PANSS score were included as the dependent variable, OCs and their subtypes, age, sex, cannabis use (yes/no), childhood adversity (yes/no) and CPZ dosage were included as the independent variables.

The Statistical Package for Social Science (SPSS) version 23.0 (IBM Corp., Armonk, NY, USA) was used for statistical analyses. All statistical tests were two-tailed, and significance was determined at the 0.05 level.
For difficulties during the whole pregnancy period, when we considered the PANSS general subscale as the dependent variable, the following independent variables, Lewis AB (F = 4.054; p = 0.045) and daily equivalent doses of CPZ (F = 7.362; p = 0.007) were significantly associated, while age (F = 0.702; p = 0.403), sex (F = 0.211; p = 0.646), cannabis use (F = 0.839; p = 0.361) and childhood adversity (F = 0.588; p = 0.444) were not associated.

For difficulties during delivery, when we considered the PANSS general subscale as the dependent variable, the following independent variables, Lewis C (F = 6.826; p = 0.010) and daily equivalent doses of CPZ (F = 7.885; p = 0.005) were significantly associated, while age (F = 0.791; p = 0.375), sex (F = 0.565; p = 0.453), cannabis use (F = 1.306; p = 0.255) and childhood adversity (F = 0.415; p = 0.520) were not associated. When considering the PANSS total scale as the dependent variable, Lewis C (F = 4.795; p = 0.030) and daily equivalent doses of CPZ (F = 10.119; p = 0.002), were significantly associated, while age (F = 0.968; p = 0.326), sex (F = 0.080; p = 0.778) cannabis use (F = 0.997; p = 0.319) and childhood adversity (F = 0.878; p = 0.350) were not.

For OCs taken all together, when considering the PANSS positive subscale as the dependent variable, Lewis T (F = 6.950; p = 0.009) was significantly associated, while daily equivalent doses of CPZ (F = 3.384; p = 0.067), age (F = 0.466; p = 0.496), sex (F = 2.027; p = 0.156), cannabis use (F = 3.113; p = 0.079) and childhood adversity (F = 0.050; p = 0.824) were not associated. When considering the PANSS general subscale as the dependent variable, the following independent variables, Lewis T (F = 7.755; p = 0.006) and daily equivalent doses of CPZ (F = 6.818; p = 0.010) were significantly associated, while age (F = 1.185; p = 0.278), sex (F = 0.947; p = 0.332), cannabis use (F = 1.065; p = 0.303) and childhood adversity (F = 0.754; p = 0.386) were not associated. Finally, when considering the PANSS total scale as the dependent variable, the independent variables Lewis T (F = 6.608; p = 0.011) and daily equivalent doses of CPZ (F = 9.053; p = 0.003) were significantly associated, while age (F = 1.434; p = 0.232), sex (F = 0.193; p = 0.661), cannabis Use (F = 0.682; p = 0.410) and childhood adversity (F = 1.375; p = 0.242) were not associated.

**Discussion**

The findings from our study show a worse psychopathological profile among people with FEP that experienced difficulties during the perinatal period compared with patients who were not exposed to them. These results confirm the association between OCs and the presentation of clinical symptomatology in a cohort of FEP. Notably, our results were not confounded by other known risk factors such as age, sex, cannabis use or stressful childhood events.

Compared with patients who were not exposed to perinatal stress, patients that experienced difficulties during delivery displayed a more severe psychopathological profile in relation to total PANSS score but also for the three subscales, positive, negative and general psychopathology. All were statistically significant except for the positive symptom subscale, which only showed a trend towards significance. However, when co-varied by all the potential confounders, only PANSS general psychopathology and total score maintained significant associations. Similar findings were observed when all the OC variables were considered. In this case, patients who presented OCs displayed a statistically significant difference in clinical profile. However, when the covariates were included in the analysis, the PANSS negative subscale did not retain its significant association, while the rest did (positive, general subscale, and childhood adversity).
and total scale score). Patients with difficulties during the whole pregnancy period also displayed a worse clinical profile, which proved significant in the general psychopathology subscale and maintained its association when covariates were included in the statistical model. Thus, in our sample, perinatal risk factors are associated with the general psychopathology subscale and the total PANSS score.

Our results are in line with previous findings; in chronic schizophrenia patients, difficulties in delivery have been associated with more severe symptomatology from the general psychopathological subscale from the PANSS (Mezquida et al., 2021), while the lower Apgar score, which is a simple and objective method evaluating the degree of birth asphyxia, was associated with negative symptoms in early-onset schizophrenia (Kotlicka-Antczak et al., 2001). Although other similar results were described, they considered OCs as a unique construct and did not differentiate between pregnancy and delivery periods (Kotlicka-Antczak et al., 2001; Borowska & Rybakowski, 2002; Jones et al., 2011). Although Mechri and associates (Mechri et al., 2008) reported that higher sub-scores were observed during the period of child-birth, no further specification was obtained in relation with psychopathology besides more severe negative symptomatology. In contrast to other studies, we did not find any difference in relation to sex (Gallagher et al., 2014). As expected, the antipsychotic dose evaluated in CPZ equivalents was also associated with the clinical psychopathology. Indeed research in animal models has studied the interaction between perinatal asphyxia and schizophrenia risk genes (Wakuda et al., 2021) and also in bipolar disorder (Haukvik et al., 2014). Indeed research in animal models has studied the interaction between perinatal asphyxia and schizophrenia risk genes (Wakuda et al., 2021; Paparelli et al., 2017). In the general population, birth asphyxia has been associated with unspecific psychopathology such as hyperexcitability, irritability, timidity, aggressiveness, reduced activity, concentration and motivation (Nabieva, 2009). Furthermore, birth asphyxia is a risk factor widely described not only for schizophrenia (Dalman et al., 2001; Pugliese et al., 2019) but also for other pathologies such as personality disorder (Fazel et al., 2012) and pervasive developmental disorders (Van Handel et al., 2007).

Several limitations need to be highlighted when considering our findings. OCs were not recorded at birth but retrospectively in a familiar interview, which has been accepted as valid in a psychosis sample (Borrajo et al., 2011). OCs were categorised from a clinical scale and further information regarding the timing and duration of the insult is required (Ellman et al., 2019). The heterogeneity of methods evaluating OCs should be considered. While our approach is based on the Lewis–Murray scale, other authors evaluated OCs with the McNeil–Sjostrom questionnaire (Mechri et al., 2008) while others directly obtained OCs from the “social history” section of the hospital records (Jones et al., 2011).

When considering all the results, we note that difficulties during delivery are more related to psychopathology than difficulties during the pregnancy period, suggesting an important effect of labour complications on patient outcomes later in life. Our results have interesting implications in terms of early intervention services/strategies in psychosis, as patients at initial stages with a background of OCs and unspecified symptomatology shall be closely monitored due to the heterogeneity of the clinical presentation of psychosis.

**Conclusions**

Our results confirm that the presence of difficulties during the perinatal period is associated with a more severe clinical presentation at onset and in the first stages of the illness. Our approach to differentiating the events according to the timing of the event distinguished the effect of difficulties during pregnancy and during

### Table 2. Comparisons between groups depending on the presence (yes) or absence (no) of obstetric complications

<table>
<thead>
<tr>
<th></th>
<th>Positive Subscale</th>
<th>Negative Subscale</th>
<th>General Subscale</th>
<th>Total scale</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No mean (SD)</td>
<td>Yes mean (SD)</td>
<td>No mean (SD)</td>
<td>Yes mean (SD)</td>
</tr>
<tr>
<td>Lewis A</td>
<td>18.44 (8.0)</td>
<td>21.27 (6.9)</td>
<td>18.84 (8.4)</td>
<td>16.53 (7.4)</td>
</tr>
<tr>
<td>Lewis B</td>
<td>18.77 (7.9)</td>
<td>20.04 (9.4)</td>
<td>18.47 (8.0)</td>
<td>21.25 (10.9)</td>
</tr>
<tr>
<td>Lewis C</td>
<td>17.81 (7.9)*</td>
<td>20.23 (8.2)</td>
<td>18.25 (8.2)*</td>
<td>21.28 (9.0)</td>
</tr>
<tr>
<td>Lewis AB</td>
<td>18.58 (7.9)*</td>
<td>21.29 (8.4)</td>
<td>18.66 (8.1)</td>
<td>19.60 (9.9)</td>
</tr>
<tr>
<td>Lewis T</td>
<td>17.59 (7.7)*</td>
<td>21.03 (8.2)</td>
<td>18.31 (8.0)*</td>
<td>20.25 (9.5)</td>
</tr>
</tbody>
</table>

<sup>*p < 0.05, *p < 0.10</sup>

Lewis A, complications of pregnancy; Lewis AB, any obstetric complication during pregnancy; Lewis B, abnormal fetal growth and development; Lewis C, difficulties in delivery; Lewis T, total; PANSS, positive and negative syndrome scale; SD, standard deviation.
delivery into different clinical areas. Our results highlight the need of describing the timing of the event during the perinatal period to better understand its impact on the clinical presentation at onset. This might help to have a greater understanding of its impact on the clinical and functional outcome, giving way to the design and the implementation of early and personalised interventions with the potential to modulate the outcome of schizophrenia following a first episode of the disease.

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References


Hales CN and Barker DJP (1992) Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. Diabetologia. https://doi.org/10.1007/BF00400248


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Appendix

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