Journal of Psychiatric Research 151 (2022) 461–468

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

Shaped before birth: Obstetric complications identify a more severe clinical phenotype among patients presenting a first affective or non-affective episode of psychosis☆

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ARTICLE INFO

Keywords:
Clinical phenotypes
Early intervention
First episode psychosis
Obstetric complications
Neurodevelopmental hypothesis

ABSTRACT

Obstetric complications (OCs) may contribute to the heterogeneity that characterizes psychiatric illness, particularly the phenotypic presentation of first episode psychoses (FEP). Our aim was to examine the relationship between OCs and socio-demographic, clinical, functioning and neuropsychological characteristics in affective and non-affective FEP. We performed a cross-sectional,study where we recruited participants with FEP between 2011 and 2021, and retrospectively assessed OCs using the Lewis-Murray scale. OCs were used as a dichotomous variable and further stratified into three subtypes: complications of pregnancy, abnormal fetal growth and development, and difficulties in delivery. We performed a logistic stepwise forward regression analysis to examine variables associated with the presence of OCs. Of the 104 participants (67 affective FEP and

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https://doi.org/10.1016/j.jpsychires.2022.05.005
Received 4 January 2022; Received in revised form 8 April 2022; Accepted 9 May 2022
Available online 17 May 2022

37 non-affective FEP), 31.7% (n = 33) had experienced OCs. Subjects with OCs showed a more gradual emergence of prodromal symptoms as well as higher negative and total Positive and Negative Syndrome Scale (PANSS) scores. In the multivariate analysis, the presence of OCs was independently associated with a younger age at first episode of any type (OR = 0.904, p = 0.003) and slower emergence of prodromal symptoms (OR = 0.274, p = 0.011). When considering specific types of OCs, those related with fetal growth were associated with worse neuropsychological performance, while OCs at delivery were related to earlier onset of illness and more severe symptoms. In conclusion, OCs signaled a specific FEP phenotype characterized by earlier and more protracted onset of illness as well as more burdensome symptoms, independently of FEP type (i.e., affective vs non-affective). These results indicate a potential target of early intervention in FEP.

1. Introduction

Obstetric complications (OCs) have been identified as a risk factor for several psychiatric disorders (Eaton et al., 2001; Fazel et al., 2012; Vasconcelos et al., 2007; Walder et al., 2014). In particular in schizophrenia (SCZ), the risk conferred by OCs is one of the key elements in the classical neurodevelopmental hypothesis, in which prenatal and perinatal brain insults, combined with genetic susceptibility, predispose to the later emergence of psychosis (Davies et al., 2020; Murray et al., 1987). The already higher risk of psychiatric disorders in the offspring of women suffering from severe mental illness increases even further when OCs are present, which is of special relevance considered that these mothers experience more prenatal and perinatal disturbances than the general population (Judd et al., 2014; Suvisaari et al., 2013).

In addition to an increased incidence of mental disorders, OCs may contribute to the heterogeneity that characterizes psychiatric illness (Mezquida et al., 2018). In fact, evidence suggests that certain clinical presentations are more prevalent in individuals with mental illness that suffered OCs compared to those that did not. For example, patients with SCZ that specifically experienced difficulties during delivery showed more severe depressive symptoms, while more broadly those with a higher prevalence of OCs were characterized by an earlier age of onset (Cannon et al., 2000; Mezquida et al., 2018; Rubio-Abadal et al., 2015). A recent systematic review concluded that OCs increase the risk of brain abnormalities that are typically found in SCZ, ranging from a decrease in gray matter volume to abnormal brain-ventricle ratios and a smaller volumes in limbic regions (Costas-Carrera et al., 2020). In patients with psychosis, OCs are also associated with poorer cognitive performance across different domains, such as verbal memory, attention, working memory, executive functions and processing speed, even though results are heterogeneous (Mittal et al., 2009; Ochoa et al., 2013; Torniainen et al., 2013). Thus, the presence of OCs might underpin specific phenotypes of psychiatric illness, which might help better explain and understand the complexity of these diseases (Mezquida et al., 2018).

The higher prevalence of prenatal and perinatal disturbances has been robustly demonstrated in first episode non-affective psychosis (Cannon et al., 2002; Davies et al., 2020) while the association is less consistent in affective psychoses, with inconclusive findings in bipolar disorder (BD) (Scott et al., 2006). Most of the research has focused on non-affective FEP and has identified a positive history for OCs to be associated with aspects of symptomatology, severity and illness course, for example negative symptoms, earlier age of onset and worse outcomes (Gallagher et al., 2014; Rubio-Abadal et al., 2015; Stathopoulou et al., 2013; Verdoux et al., 1997). Less is known on the outcomes associated with OCs in first affective psychoses. In an Irish register study, age at first diagnosis was not related to the presence of OCs in patients hospitalized for a manic episode (Browne et al., 2000), while another study showed that patients with early-onset BD were significantly more likely to have experienced OCs compared with individuals with late-onset disease (Guth et al., 1993). However, psychotic and mood disorders seem to share distinctive disease characteristics when OCs are present (Arango et al., 2014; Buoli et al., 2016). Interestingly, Buoli and colleagues (Buoli et al., 2016) identified that perinatal problems contributed to differential characteristics independently of the diagnosis (i.e., SCZ or BD). In particular, a Finnish study identified that individuals reporting abnormal fetal growth -namely those being born small- had significantly increased risks of any mental and substance use disorders (Lahti et al., 2015).

1.1. Aims of the study

The aim of this study was to examine the relationship between obstetric complications and socio-demographic, clinical, functioning and neuropsychological characteristics in individuals with a first-episode psychosis. We hypothesized that the presence of obstetric complications would be associated with a specific first-episode psychosis phenotype, characterized by more severe symptoms and worse clinical outcomes.

2. Material and methods

2.1. Participants

This is a cross-sectional, multicentric study including the Bipolar and Depressive Disorders Unit of IDIBAPS-Hospital Clínic in Barcelona, FIDMAG Research Foundation and the Institut Pere Mata, under the umbrella of the Spanish Research Network on Mental Health (CIBERSAM) (Fraguas and Díaz-Calleja, 2021; Salagre et al., 2019). We recruited participants with both affective and non-affective first episode of psychosis (FEP) between 2011 and 2021. The inclusion criteria for FEP patients were: (i) age between 18 and 45 years at the time of first evaluation; (ii) having experienced their FEP during the previous four years; and (iii) being in full or partial clinical remission (i.e., after discharge from the hospital).

Exclusion criteria were the presence of (i) a mental intellectual disability (defined as intelligence quotient [IQ] <70); (ii) presence of any medical condition affecting neuropsychological performance; (iii), alcohol/substance dependence in the previous year to study inclusion (excluding caffeine and tobacco); (iv) having received electroconvulsive therapy (ECT) in the 12 months before participation.

The study was carried out following the latest version of the Declaration of Helsinki and it was reviewed by the ethical committee of the three recruiting centers. Participants gave written informed consent.

2.2. Procedures

Participants were recruited from hospitalization and ambulatory settings from the three recruiting centers. OCs were evaluated retrospectively with the Lewis-Murray scale (Lewis and Murray, 1987) and were coded as a dichotomous variable (yes/no) and also dividing them into three subtypes, as proposed by Cannon et al. (2002): (a) complications of pregnancy (syphilis, rubella, Rh disease, severe preeclampsia, bleeding before delivery, threatened abortion), (b) abnormal fetal growth and development (twin delivery, preterm birth of <37 weeks, post-term birth of >42 weeks, low birth weight of <2500 g, any congenital physical anomaly), and (c) difficulties in delivery (prelabor rupture of membranes, labor of >36 h or <3 h, umbilical cord prolapse, complicated cesarean delivery, abnormal fetal presentation, use of

forceps, use of an incubator >4 weeks, hypoxia). Information regarding OCs was obtained through interviews with the patients and their parents (when available), and medical records were assessed for completeness of information. Some patients presented with more than one OC; for the purpose of the present study, we considered each OC separately. Socio-demographic data including age, educational level or working status, among others, were collected and stored in an electronic data repository. Parental socioeconomic status (SES) was determined using Hollingshead's Two-Factor Index of Social Position (Hollingshead and Redlich, 2007).

All patients were assessed using a semi-structured interview based on the Structured Clinical Interview for DSM Disorders (SCID-I-II) (First, 1997; First et al., 1997) and diagnoses were determined according to DSM-5 criteria (American Psychiatric Association, 2013). Patients who presented at least two of the five symptoms of the criterion A for a DSM-5 psychotic disorder and not experienced the DSM-5 A-D criteria for a manic episode or the DSM-5 A-E criteria for a major depressive episode with psychotic features were categorized as a non-affective FEP. Patients meeting the DSM-5 A-D criteria for a manic episode or the DSM-5 A-E criteria for a major depressive episode with psychotic features were categorized as affective FEP. Clinical information on onset features (i.e., age at onset, age at first hospitalization) were collected. We evaluated clinical symptoms with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), the Young Mania Rating Scale (YMRS) (Young et al., 1978) and the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979). Higher scores indicate greater severity. Information on the current pharmacological treatment was also gathered. Current psychosocial functioning was assessed through the Functional Assessment Short Test (FAST) (Rosa et al., 2007; Amoretti et al., 2021). The Premorbid adjustment, namely levels of functioning before the onset of illness, was assessed with The Premorbid Adjustment Scale (PAS) (Cannon-Spoor et al., 1982). Only childhood and early adolescence life periods were taken into account for PAS. Higher scores of both FAST and PAS indicate worse functioning.

The pattern of presentation of prodromal symptoms was evaluated using categories derived by Correll and colleagues (Correll et al., 2014), describing onset and the deterioration patterns. The onset pattern of the prodromal period was defined as "gradual" if $\geq$ 4 months or "rapid" if $<$ 4 months. The deterioration pattern was defined as "slow" if $\geq$ 4 weeks and "rapid" if $<$ 4 weeks. Three different patterns of presentation were then derived, namely 1 = gradual onset with slow deterioration; 2 = gradual onset with rapid deterioration; and 3 = rapid onset with rapid deterioration or abrupt.

In addition, information on the presence of a positive family history for non-affective psychosis and BD was assessed. Information on previous contact with mental health services and the use of cannabis before the onset were also collected. Finally, the Duration of Untreated Psychosis (DUP) was calculated as the number of days between the first manifestations of psychotic symptoms and the initiation of antipsychotic treatment.

All patients underwent a neuropsychological assessment when they were stable or in partial remission. The neuropsychological battery measured the following cognitive domains: 1. Estimated intelligence quotient (IQ), assessed with the Wechsler Adult Intelligence Scale (WAIS-III) (Weschsler, 1955) vocabulary subtest; 2. Working memory index of the WAIS-III, derived from the performance on the Digit Span, Arithmetic and Letter-Number Sequencing subtests; 3. Processing speed index of the WAIS-III (Digit Symbol and Symbol Search subtests); 4. Verbal learning and memory, assessed with the California Verbal Learning Test (CVLT) (Delis et al., 1993); 5. Logical memory, evaluated using the Wechsler Memory Scale, 3rd edition (WMS-III) (Wechsler, 1997); 6. Executive function, evaluated using the Wisconsin Card Sorting Test (WCST) (Berg, 1948); 7. Sustained attention, tested with the Continuous Performance Test–II (CPT-II), version 5 (Conners, 2005); and 8. Verbal fluency (phonemic and semantic), assessed with the Controlled Oral Word Association Test (COWAT) (Benton, 1967). All scores were standardized with respect to the subject's age and/or educational level according to standardized normative data found in the test manual. Higher scores correspond to better performance in all cognitive domains except for attention. All assessments were performed by a trained psychiatrist or psychologist.

2.3. Statistical analysis

We used mean and standard deviation (SD) for continuous variables and number of subjects (N) and percentage (%) for categorical data.

Principal Component Analysis (PCA) was performed for neuropsychological variables, in order to avoid redundant information of separate test cognitive variables (e.g., free recall and semantic cued recall -Short and Long Delay-of CVLT) and reduce measures to a few principal domains. The neurocognitive assessment was represented by five factor scores (verbal memory -measure of list-learning-, logical memory -story-based verbal task-, executive function, sustained attention and verbal fluency) (Supplementary Table 1), two indexes of the WAIS-III (working memory and processing speed) and an estimated IQ.

Differences between subjects with and without OCs were calculated with χ^2, Fisher's exact test and Student's t-tests when applicable.

The comparison of the subgroups of OCs were performed between those subjects without OCs and those with each subgroup of OCs, excluding the subjects from the remaining subgroups. Regarding complications of pregnancy, due to the small sample size (n = 4) we decided not to evaluate differences between groups.

We then divided the sample based on type of first episode (affective/non-affective) and evaluated separately the association with the variables for which significant differences were identified between subjects with and without OCs. This was of special relevance for age at onset of FEP, as it is well known that BD has a later age of onset than SCZ (Kennedy et al., 2005; Kessler et al., 2007).

Also, in order to ensure that sex was not acting as an effect modifier in terms of negative symptomatology as suggested by earlier research -which pointed at a female-specific connection between OCs and negative symptoms- (Gallagher et al., 2014), we stratified the sample by sex.

To further analyze the variables associated with the presence of OCs, we performed a stepwise forward logistic regression analysis including the variables that were (i) significant in bivariate analysis, (ii) coherent with past research or (iii) without a well-defined knowledge and, thus, worthy of being explored, using the presence of OC as the dependent variable. Odds ratio (OR) and 95% confidence interval (CI) were calculated. Receiver operating characteristic (ROC) analyses were used to evaluate the performance of the model.

We conducted the analyses with the Statistic Package for Social Sciences (SPSS version 25 for Windows). We set the significance level at $p \leq 0.05$. All tests were two-tailed.

3. Results

3.1. Sample description

The sample consisted of 104 subjects with a mean age of 27.1 years (SD 6.7, range 18–43), 51.9% of which were males. Sixty-four percent (n = 67) were affective FEP and 35.6% (n = 37) were non-affective FEP. Thirty-one percent (n = 33) had experienced OCs (17 affective and 16 non-affective FEP), which included: (a) complications of pregnancy in 3.8% (n = 4), (b) abnormal fetal growth and development in 9.6% (n = 10) and (c) difficulties in delivery in 24% (n = 25).

3.2. Characteristics associated with OCs

Socio-demographic characteristics were not statistically different between OCs groups, except for younger age in those who had suffered from OCs (24.6 ± 5.5 versus 28.3 ± 6.9, mean difference -MD- = 3.345, CI 0.916–6.375) (Table 1).

Table 1
Socio-demographic, clinical, functional and neuropsychological characteristics of the study group on the presence of obstetric complications.

	No OC (n = 71, 68.3%)	OC (n = 33, 31.7%)	Test (X^2, Fisher's F or Student's t)	p-value
Socio-demographic variables				
Age (years), mean (SD)	28.3 (6.9)	24.6 (5.5)	2.649	0.009
Sex, N (%)			0.072	0.789
Male	38 (53.5)	16 (48.5)		
Female	33 (46.5)	17 (51.5)		
Socioeconomic status, N (%)			4.903	0.261
V *(lowest)*	21 (30)	11 (35.5)		
IV	17 (24.3)	7 (22.6)		
III	11 (15.7)	5 (16.1)		
II	9 (12.9)	7 (22.6)		
I *(highest)*	12 (17.1)	1 (3.2)		
Civil status (married), N (%)	12 (16.9)	4 (12.1)	0.113	0.636
Education, N (%)			1.431	0.869
Primary	3 (4.2)	3 (9.1)		
Secondary	40 (56.4)	16 (48.5)		
Tertiary	28 (39.4)	14 (42.4)		
Clinical variables				
Type of First Psychotic episode, N (%)			2.737	0.098
Affective	50 (70.4)	17 (51.5)		
Non-affective	21 (29.6)	16 (48.5)		
Age of psychiatric hospitalization for a First Psychotic episode, mean (SD)	27.2 (6.9)	23.5 (5.8)	**2.549**	**0.012**
Age at First Psychotic episode, mean (SD)	27.5 (6.8)	23.9 (5.9)	**2.560**	**0.012**
Age at first lifetime episode, any type, mean (SD)	24.7 (7.4)	20.1 (7.2)	**2.957**	**0.004**
Previous contact with mental health services (yes), N (%)	40 (56.3)	22 (75.9)	2.554	0.110
Cannabis use prior to first episode (yes), N (%)	52 (73.2)	21 (63.6)	1.127	0.566
Pattern of presentation of prodromal symptoms, N (%)			**10.665**	**0.004**
Gradual/Slow (yes), N (%)	20 (28.2)	16 (48.5)		
Gradual/Rapid (yes), N (%)	47 (66.2)	11 (33.3)		
Abrupt (yes), N (%)	4 (5.6)	6 (18.2)		
Family history of primary non-affective psychosis (yes), N (%)	14 (20.3)	6 (18.2)	0.000	1.000
Family history of bipolar disorders (yes), N (%)	16 (23.2)	8 (24.2)	0.000	1.000
Duration of untreated psychosis, mean (SD)	42.1 (77)	90.6 (210.8)	−1.201	0.239
Current pharmacological treatment, yes, N (%)				
Antipsychotics	47 (66.2)	24 (72.7)	0.193	0.660
Lithium	43 (60.6)	14 (42.4)	2.305	0.129
Other mood stabilizers	8 (11.3)	3 (9.1)	0.000	1.000
YMRS, total, mean (SD)	1.5 (1.9)	2.1 (3.4)	−1.070	0.287
MADRS, total, mean (SD)	6.3 (4.9)	8.5 (7.6)	−1.511	0.138
PANSS, positive symptoms, mean (SD)	8.1 (2.4)	9.8 (4.5)	−2.009	0.051
PANSS, negative symptoms, mean (SD)	11.1 (5.5)	14.4 (7.1)	**−2.335**	**0.024**
PANSS, general, mean (SD)	2352 (6.3)	26.6 (8.6)	−1.798	0.078
PANSS, total, mean (SD)	42.8 (12.0)	50.7 (18.2)	**−2.279**	**0.027**
Psychosocial functioning				
PAS (premorbid adjustment), total, mean (SD)	12.9 (7.9)	14.1 (8.8)	−0.672	0.503
FAST (current functioning), total, mean (SD)	21.4 (13.5)	19.2 (13.3)	0.759	0.450
Neuropsychological variables				
Intellectual quotient			−0.754	0.453
	103.8 (12.5)	106.1 (11.7)		
Working memory	91.4 (15.3)	94.4 (15.8)	−0.754	0.453
Processing speed	98.9 (17.1)	93.9 (16.8)	1.148	0.254
Verbal memory	215.3 (57.4)	217.4 (37.5)	−0.184	0.854
Logical memory	201.8 (43.1)	189.9 (46.2)	0.925	0.358
Executive function	102.2 (18.7)	102.7 (14.7)	−0.122	0.903
Sustained attention	89.0 (8.4)	89.9 (11.1)	−0.355	0.723
Verbal fluency	78.4 (15.9)	79.8 (16.5)	−0.340	0.734

FAST: Functional Assessment Short Test. HDRS: Hamilton Depression Rating Scale. MADRS: Montgomery-Asberg Depression Rating Scale. N: frequency. OC: Obstetric Complications. PANSS: Positive and Negative Syndrome Scale. PAS: Premorbid Adjustment Scale. SD: Standard Deviation. YMRS: Young Mania Rating Scale.

A gradual/slow pattern of presentation of prodromal symptoms was more prevalent among the group of patients with OCs (48.5% versus 28.2%, p = 0.004), and PANSS negative and total scores were higher (14.4 ± 7.1 versus 11.1 ± 5.5, MD = 3.262, CI 6.066-0.458; 42.8 ± 12 versus 50.7 ± 12.2, MD = 7.947, CI 14.967-0.927). Ages of first psychiatric hospitalization for a FEP, age at first psychotic episode and age at first lifetime of any type of episode were also significantly lower (23.5 ± 5.8 versus 27.2 ± 6.9 years, MD = 3.705, CI = 0.818–6.592; 23.9 ± 5.9 versus 27.5 ± 6.8 years, MD = 3.511, CI = 0.791–6.231; 20.1 ± 7.2 versus 24.7 ± 7.4, MD = 4.555, CI = 1.497–7.612). No significant differences were found in terms of psychosocial functioning or neuropsychological variables (Table 1).

In the stratification by type of FEP (affective/non-affective) (Supplementary Table 2), the directionality of association was maintained for all variables but was not always statistically significant. In particular, both groups maintained the directionality regarding age at onset of FEP (namely, earlier age at onset when OCs were present), showing a tendency to significance in affective FEP (27.1 ± 7.2 versus 23.8 ± 5.4, p = 0.097), and being significant in non-affective FEP (28.4 ± 5.5 versus 24.1 ± 6.6, MD = 4.318, CI 0.285–8.351).

In terms of stratification by sex (performed in order to ensure that sex was not a confounding factor regarding negative symptoms, as previously mentioned) directionality of association was maintained in both groups –i.e., worse negative symptomatology punctuations when OCs were present-, although it did not reach statistical significance in either group (PANSS negative scores in males: 11.1 ± 6.1 versus 15.6 ± 8.5, p = 0.65; and females: 11.2 ± 4.7 versus 13.2 ± 5.4, p = 0.18).

The logistic regression model contained three independent variables (age at FEP, pattern of presentation of prodromal symptoms and PANSS total symptoms score) (Supplementary Table 3). The full model containing all variables was statistically significant, $\chi 2$ (3, N = 104) = 21.226, p < 0.001. The model as a whole explained between 19% (Cox and Snell R square) and 26.4% (Nagelkerke R squared) of the variance in OCs, and correctly classified 71.3% of cases. Overall, sensitivity was 42.4%, whilst its specificity was 85.3%. The positive predictive value was 58.3% and the negative predictive value was 75.3%. The presence of OCs was independently associated with a younger age at first lifetime episode of any type (OR = 0.904, p = 0.003) and a different pattern of presentation of prodromes (more probably slower than rapid, OR = 0.274, p = 0.011). The ROC analysis supported the utility of the model and its variables, as it performed significantly better than chance in predicting the association between predicting variables and OCs, with

an area under the curve (AUC) = 0.76 (CI 0.66–0.86). (Supplementary Fig. 1).

3.2.1. Subgroups of OCs

Compared to those without OCs (n = 71), the subgroup with abnormal fetal growth and development (n = 10) showed worse attention (89 ± 8.4 versus 96.8 ± 11, t = −2.244, p = 0.028, MD = 7.76, CI 0.85–14.68) and lower processing speed performance (98.9 ± 17.1 versus 80.4 ± 13.8, p = 0.08, t = 2.746, MD = 18.43, CI 5.04–31.82). No differences on socio-demographic and clinical variables, psychosocial functioning and other neuropsychological variables were found.

Regarding the subgroup of difficulties in delivery (n = 25), their age was lower (28.3 ± 6.9 versus 24.4 ± 5.8, t = 2.560, p = 0.014, MD = 3.882, CI 0.807–6.957), and also their age at first hospital admission (27.2 ± 6.9 versus 23.1 ± 6.0, t = 2.505, p = 0.014, MD = 4.147, CI 0.854–7.440) and age at first psychotic episode (27.5 ± 6.8 versus 23.8 ± 6.1, t = 2.4, p = 0.018, MD 3.691, CI 0.637–6.744, respectively). In addition, their negative PANSS scores were higher (11.1 ± 5.5 versus 14.6 ± 7.7, t = −2.078, p = 0.045, MD = 3.468, CI 0.074–6.861). Neurocognitive variables did not show statistically significant differences.

4. Discussion

Our study examined the relationship between OCs and sociodemographic, clinical, functioning and neuropsychological characteristics of individuals with a FEP. Our main findings suggest that OCs are associated with a specific clinical phenotype characterized by an earlier and more protracted onset of illness and a higher burden of clinical symptoms, which is independent from the type of FEP (i.e., affective and non-affective). When considering specific type of OCs, those related to fetal growth were associated with worse neuropsychological performance, while OCs at delivery were found to be more frequently associated with earlier onset of illness and more severe symptoms.

Our results indicate that OCs may contribute to the clinical course of FEP. Earlier age of onset has previously been well documented, especially regarding non-affective psychosis (Rubio-Abadal et al., 2015; Verdoux et al., 1997). Particularly, patients with onset of SCZ before age 22 had more often a history of acute fetal distress, with abnormal presentation at birth and complicated cesarean delivery (Boog, 2004), in line with the results of our study. In addition, we identified for the first time an association with a slower progression of prodromic symptoms. This finding is consistent with the higher -although not statistically significant-previous contact with mental health services of the OCs group and, most important, it appears biologically plausible. It also points out the need for an especially thorough follow-up of those subjects that had suffered from OCs and present with potentially prodromal symptoms, since they may be at a greater risk of transition (Kotlicka-Antczak et al., 2018). Similarly, mothers with genetic risk of psychosis could specially benefit from specific interventions that lower the risk of obstetric complications, such as the recent proposal of Crovetto et al. (2021). In addition, OCs were associated with a higher burden of symptoms, especially of the negative spectrum, which is coherent with previous findings (Kotlicka-Antczak et al., 2001; Ruiz-Veguilla et al., 2008; Stathopoulou et al., 2013; Verdoux et al., 1997). It is of note, however, that sex did not modulate this relationship in our sample, contrary to the female-specific connection between OCs and negative symptomatology that was described by Gallagher et al. (2014). Nevertheless, recent research highlighted the effect not only of sex but also of the timing of the exposure as a modulator of the clinical outcome (Ellman et al., 2019). Moreover, a younger age of onset and more severe negative symptoms have repeatedly been associated, including in a recent meta-analysis in patients with SCZ (Immonen et al., 2017); this association might be explained, at least partially, with an antecedent of OCs. That said, we did not find differences in premorbid adjustment or current psychosocial functioning -measured by PAS and FAST scales-based on the presence of OCs, which is surprising considering the widely reported association both with negative symptomatology and earlier onset of disease (Griffiths et al., 2019; Verdolini et al., 2021; Stouten et al., 2017). Our sample size might have limited our ability to identify a significant difference, and PAS results showed directionality towards worse premorbid adjustment in the group with OCs.

In terms of neurocognitive assessment, there were no global differences between subjects that had experienced OCs and those who had not. Differences, however, were identified when we analyzed the sample divided by subtype of OCs. Individuals with abnormal fetal growth and development showed poorer cognitive performance in terms of attention and processing speed. Deficits in the mentioned cognitive domains are a well-known characteristic of both SCZ (Knowles et al., 2010) and BD (Daban et al., 2012). Thus, complications related to abnormal fetal growth and development might exacerbate these impairments and/or act as triggers, leading to worse performances in these already impaired cognitive domains. The timing of the exposure to the OC is considered to modulate outcomes in patients (Ellman et al., 2019); for example, maternal infection during pregnancy has been described to affect cognition in offspring (Brown et al., 2009, 2011; Ellman et al., 2009), and low birth weight has been associated with lower cognitive performance (Torniainen et al., 2013). In particular, a study that assessed the association between low birth weight and cognitive performance in SCZ found that it was associated with lower performance in visuospatial reasoning, processing speed, set-shifting and verbal and visual working memory (Torniainen et al., 2013). Also, in general population it has been shown that birth weight was associated with attention (Petersen et al., 1990). In fact, a systematic review and meta-analysis that included 19 studies of the association between normal BW and general cognitive ability in non-clinical adult population concluded that there is a modest association between BW and cognitive ability (Grove et al., 2017).

Finally, regarding again the subgroups of OCs, our findings suggest that worse symptomatology is present across subgroups, whereas earlier age at onset is more related to difficulties in delivery.

Our study presents several limitations. First, the presence of OCs was collected retrospectively, which might affect accuracy, although there is evidence suggesting it might not (Borrajo et al., 2011; Walshe et al., 2011). Second, the study considered OCs as dichotomous, although we also explored the different subtypes of OCs. Yet the analyses of subgroups of OCs might have been underpowered, given the relatively small samples sizes. This also prevented us to perform logistic regression analyses in these subgroups and bivariate analyses in the subgroup of complications of pregnancy. Third, the group of non-affective FEP patients was smaller, which might have influenced the assessment of differences between groups in terms of the presence of OCs. Fourth, as recruitment age was limited to those of 18 years or older, our study provides insight into adult FEP only. Fifth, we might have been unaware of unmeasured confounding variables, so we cannot rule out the potential for residual confounding in our study. More extensive and detailed studies would help confirming the findings. Finally, the observational nature of the study prevents from causal inference. Therefore, the presence of OCs might be a possible hit in the neurodevelopment of the patient and we observed that is associated with a more severe clinical phenotype at the time the patient presents his/her first psychotic episode, but we certainly cannot infer causality.

Despite these limitations, our study has several strengths that are worth mentioning. A relevant one is the similarity of basal characteristics between those with and without OCs in terms of potential confounding variables in relation to psychosis, such as cannabis use or family history of SCZ or BD. Also, the clinical sample is relatively large considering the exhaustive clinical and cognitive assessments that were performed, which lead to the inclusion of variables that are seldom assessed, such as the rapid or gradual onset of psychotic symptoms. Furthermore, we decided to focus on the clinical expression of the presence of OCs independently from the diagnosis (i.e., BD, SCZ, schizoaffective disorder). It allowed us to identify a common phenotype

already suggested by previous findings (Buoli et al., 2016) that has potential clinical implications in terms of strengthening clinical attention during the prodromal phase -as means of secondary prevention. It also emphasizes the value of adequate obstetric care -as means of primary and tertiary prevention-. In the same line, an exhaustive evaluation of OCs in high-risk populations for FEP may be advisable in order to tailor specific early intervention strategies, such as a more intensive psychoeducation for patients and families and a tighter schedule of follow-up visits. Furthermore, cognitive reserve enhancement strategies as well as functional remediation would be of help, depending on the clinical presentation (De la Serna et al., 2021). Currently, there is a trend to introduce early intervention strategies at the very first opportunity (Vieta and Berk, 2022).

5. Conclusions

In conclusion, our results suggest that OCs might be associated with a specific phenotypical FEP presentation, characterized by a longer prodromal phase, earlier age of onset and higher burden of disease (Garcia-Rizo and Bitanihirwe, 2020), which seems also modulated by the moment of gestation in which the noxious hit was produced. Thus, considering the potential role of OCs on early identification of clinical phenotypes, they might help personalize treatment strategies for these patients.

Author statement

MSV: conceptualization, data curation, formal analysis, investigation, methodology, project administration, Roles/Writing - original draft.

NV and SA: supervision, resources, conceptualization, formal analysis, investigation, methodology, project administration, Roles/Writing - original draft.

MG, GM, EW, MSN, MFF, CV, LM,RPG, SM, GS, GA, GF, AGP, MTPC, PSP, IMS, VSG, EPC, JARQ, JU, MR, AMA, IP, IV, MB, CGR, EV: resources, writing - review & editing.

Role of the funding source

The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Declaration of competing interest

MSV has received financial support for CME activities and travel funds from Janssen-Cilag and Lundbeck, and reports no financial or other relationship relevant to the subject of this article.

MG has received grants and served as consultant or advisor for Ferrer, Lundbeck, and Janssen-Cilag.

JARQ was on the speakers' bureau and/or acted as consultant for Eli-Lilly, Janssen-Cilag, Novartis, Shire, Takeda, Bial, Shionogui, Lundbeck, Almirall, Braingaze, Sincrolab, Medice and Rubió, Raffo in the last 5 years. He also received travel awards (air tickets + hotel) for taking part in psychiatric meetings from Janssen-Cilag, Rubió, Shire, Takeda, Shionogui, Bial, Medice and Eli- Lilly. The Department of Psychiatry chaired by him received unrestricted educational and research support from the following companies in the last 5 years: Eli-Lilly, Lundbeck, Janssen-Cilag, Actelion, Shire, Ferrer, Oryzon, Roche, Psious, and Rubió.

GA has received CME-related honoraria, or consulting fees from Janssen-Cilag, Lundbeck and Angelini with no financial or other relationship relevant to the subject of this article.

GF has received CME-related honoraria, or consulting fees from Angelini, Janssen-Cilag and Lundbeck.

AGP has received CME-related honoraria, or consulting fees from Angelini, Janssen-Cilag and Lundbeck.

MTPC has received support for CME activities and travel funds from Janssen-Cilag and Lundbeck, with no financial or other relationship relevant to the subject of this article.

AMA has received funding for research projects and/or honoraria as a consultant or speaker for the following companies and institutions (work unrelated to the topic of this manuscript): Otsuka, Pfizer, AstraZeneca, Bristol-Myers Squibb, Lundbeck, the Spanish Ministry of Economy and Competitiveness and Instituto de Salud Carlos III.

IP has received CME-related honoraria, or consulting fees from ADAMED, Janssen-Cilag and Lundbeck.

MB has been a consultant for, received grant/research support and honoraria from, and been on the speakers/advisory board of ABBiotics, Adamed, Angelini, Casen Recordati, Janssen-Cilag, Menarini, Rovi and Takeda.

CGR has received honoraria/travel support from Adamed, Angelini, Casen-Recordati, Janssen-Cilag and Lundbeck.

EV has received grants and served as consultant, advisor or CME speaker for the following entities (unrelated to the present work): ABBiotics, Abbott, Allergan, Angelini, Dainippon Sumitomo Pharma, Ferrer, Gedeon Richter, Janssen, Lundbeck, Otsuka, Sage, Sanofi-Aventis, and Takeda.

NV has received financial support for CME activities and travel funds from the following entities (unrelated to the present work): Angelini, Janssen, Lundbeck, Otsuka.

The rest of authors report no biomedical financial interests or potential conflicts of interest related to the present article.

VSG has received financial support for CME activities and travel funds from Janssen-Cilag, Osuka and Lundbeck, and reports no financial or other relationship relevant to the subject of this article.

Acknowledgment

We are extremely grateful to all the participants. The authors would like to thank the support of the Spanish Ministry of Science and Innovation; the CIBER of Mental Health (CIBERSAM); the Secretaria d'Universitats i Recerca del Departament d'Economia i Coneixement (2017 SGR 1365; 2017-SGR-1271) and the CERCA Programme / Generalitat de Catalunya.This work has been also supported by the Spanish Ministry of Science, Innovation and Universities integrated into the Plan Nacional de I+D+I y cofinanciado por el ISCIII-Subdirección General de Evaluación y el Fondo Europeo de Desarrollo Regional (FEDER) through a 'Miguel Servet' postdoctoral contract (CPI14/00175 to CT), a Miguel Servet II contract (CPII19/00018 to CT, CPII16/00018 to EP-C), a 'Río Hortega' contract (CM19/00123 to ES), a 'Sara Borrell' (CD20/00177 to SA), both co-funded by European Social Fund "Investing in your future", and the FIS grants (PI12/0091 to EV and JU, PI15/00283 and PI18/00805 to EV, PI18/01001 to IP and PI20/00661 to CGR).This work has been also supported by the PERIS projects SLT006/17/00357 and SLT006/17/00345 in the "Pla estratègic de Recerca i Innovació en Salut 2016–2020" (Health Department), by the ANID-PIA-ACT192064, ANID-FONDECYT 1180358, 120060 to JU, by the Agency for Management of University and Research Grants-AGAUR (Beatriu de Pinós grant to MR), and by the BITRECS project to NV and IV, which has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 754550 and from "La Caixa" Foundation (ID 100010434), under the agreement LCF/PR/GN18/50310006.GA receives research support by a Pons Bartran 2020 grant (PI046549).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2022.05.005.

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