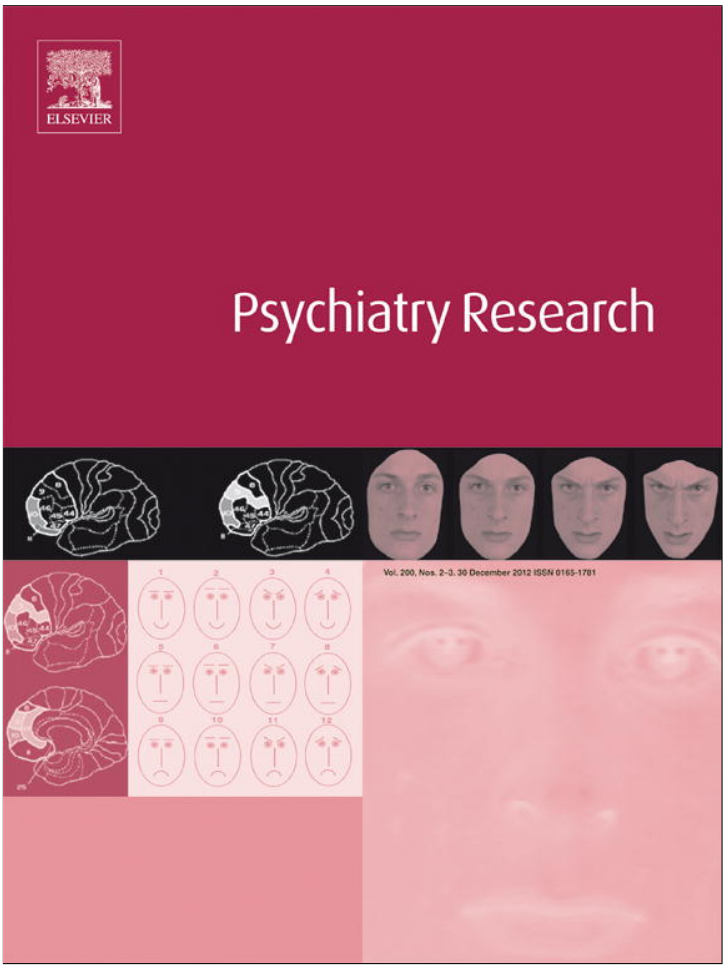

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Obstetric complications in early psychosis: Relation with family history of psychosis ☆

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ABSTRACT

The people classified as being at ultra-high risk (UHR) of developing psychosis are expected to share many risk factors for psychosis with the patients diagnosed with schizophrenia, including an enhanced incidence of obstetric complications (OCs). This study set out to investigate the incidence and correlates of OCs in a sample of patients accessing an early intervention center. Patients' mothers were asked whether they had suffered from any somatic complication during pregnancy from a list of OCs with potential direct relevance to the physical wellbeing of the offspring. Out of 86 patients diagnosed with first-episode psychosis, 20 (23%) cases were positive for the occurrence of severe OCs, as reported by their mothers during an interview; out of 83 UHR patients, 21 (25%) cases were positive for OCs. OCs were more common in individuals with a family history of psychosis than in those without such a history. OCs might interact with genetic vulnerability to increase the risk of psychosis. Lack of comparison to healthy controls is a limitation that decreases the value of these findings.

1. Introduction

Obstetric complications (OCs) are among the best-documented environmental indicators of the risk of schizophrenia, particularly hypoxia-related events (Cannon et al., 2000, 2002; Zornberg et al., 2000), but their role in the etiology of schizophrenia is still poorly understood (Tsuang, 2000; Mueser and McGurk, 2004; Mittal et al., 2008; Brown, 2011). There is some evidence that OCs might interact with genetic vulnerability to increase the risk of the disorder (Mueser and McGurk, 2004; Walshe et al., 2005; Mittal et al., 2008). However, little evidence is available on the role of OCs in people classified as being at ultra-high risk (UHR) of developing psychosis. This recently defined category includes people with signs of incipient psychosis, and principally involves three clusters of subjects: young people with attenuated positive symptoms, as revealed by dedicated interviews (Olsen and Rosenbaum, 2006); people with diagnosable transient psychotic symptoms, not stabilized in a syndrome yet (Simon et al., 2006; Phillips et al., 2007); and a third category of people with genetic risk (first degree relatives of subjects with psychosis), or meeting the criteria for Schizotypal Personality Disorder, who are showing symptoms of deterioration (Cornblatt et al., 2003). There is evidence that focused treatments with UHR people are effective in reducing the risk of transition to full-blown psychosis over a 12 month period (Preti and Cella, 2010). So, there is ground in identifying help-seeking UHR people and offering focused treatment to them.

Were OCs a specific risk factor for psychosis, their incidence should be higher in patients diagnosed with first-episode psychosis (FEP) than in UHR people, since only a minority of them develops full-blown psychosis (de Koning et al., 2009). Moreover, among the patients classified as UHR, those who convert to psychosis should show a higher incidence of OCs than those who do not convert to psychosis.

Evidence on the role of OCs in early psychosis is sparse. In a study carried out in Spain, 102 children and adolescents who developed early psychosis had a higher prevalence of OCs than 94 putatively healthy controls, taking into account socio-economic

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status and family psychiatric history (Moreno et al., 2009). In the Avon Longitudinal Study of Parents and Children (ALSPAC), adverse prenatal and perinatal events were found to be associated to higher incidence of non-clinical psychotic-like experiences at the age of 12; maternal infections during pregnancy, maternal diabetes, need for resuscitation at birth and 5-min Apgar score were the strongest predictors (Zammit et al., 2009). As for people diagnosed at ultra-high risk of psychosis, one study found a higher incidence of OCs in UHR cases ($N=52$; OCs=46%) compared to healthy controls ($N=43$; OCs=19%), but a similar proportion of OCs in FEP ($N=19$; OCs=39%) and in UHR (Ballon et al., 2008). One study found a higher risk of conversion to psychosis in UHR people with a history of OCs than in UHR people without a history of OCs (Mittal et al., 2009), while another study failed to find a link between OCs and conversion to psychosis in 74 UHR people (Yun et al., 2005). A retrospective study on 122 patients diagnosed with first-episode DSM-IV schizophrenia spectrum disorders found that childhood Attention Deficit/Hyperactive Disorder symptoms were predicted by OCs and neurodevelopmental delay, further suggesting a role of OCs in the pathways that lead from delayed milestones attainment and early symptoms in childhood, to the onset of a schizophrenia-related psychosis (Peralta et al., 2011). "Pandysmaturation", a special form of early abnormal neurodevelopment, characterized by retarded cranial development in the first year of life and delay in early motor milestone attainment, was related to schizophrenia-spectrum disorder in young adulthood in subjects at genetic risk in a sample including 75 "high-risk" offsprings of women with a history of schizophrenia or affective psychosis and 91 offsprings devoid of genetic risk for psychosis (McNeil et al., 2011).

This study set out to investigate the incidence and correlates of OCs in a sample of patients accessing for the first time the *Programma2000*, a comprehensive program targeted at the early detection of and early intervention on subjects at the onset of psychosis operating in Milan (Italy) since 1999 (Cocchi et al., 2008; Meneghelli et al., 2010). Obstetric complications were compared between patients diagnosed with a first episode of psychosis and subjects classified to be at ultra-high risk of psychosis according to the criteria developed by the Personal Assessment and Crisis Evaluation (PACE) Clinic in Melbourne (see methods for details) (Yung et al., 1996; Phillips et al., 2007). Incidence of OCs was expected to be higher in patients diagnosed with FEP than in UHR cases. The impact of OCs on outcome at 1-year in both FEP and UHR cases was investigated, too, since the patients who suffered from OCs were described to have a poorer response to treatment than those who did not (Smith et al., 1998; Alvir et al., 1999). The duration of untreated psychosis (DUP), defined as the length of time from the first onset of psychotic symptoms to access to care and/or initiation of adequate treatment, was also linked to short- (Fusar-Poli et al., 2009) and long-term outcome in schizophrenia (Marshall et al., 2005; Perkins et al., 2005). So, the links between OCs and DUP were investigated as a possible confounding factor in the relationship between OCs and 1-year outcome in FEP patients. OC frequency was reported as being higher in males than females (Geddes and Lawrie, 1995; Preti et al., 2000). Moreover, the patients who developed schizophrenia after OCs were reported to have had earlier onset of the disorder compared to those who had no OCs (O'Callaghan et al., 1992; Verdoux et al., 1997). Therefore, in investigating the links between OCs and diagnosis or 1-year outcome in FEP and UHR cases, the role of gender and age at presentation was investigated as well.

Main aims of the study were: (a) to assess whether FEP patients had higher incidence of OCs than UHR patients; (b) to assess whether sex, age and/or family history of psychosis, as a proxi of genetic vulnerability, was related to a history of OCs in the patients; (c) to assess whether OCs negatively impact on outcome at 1-year in both FEP and UHR cases.

2. Methods

Data were collected during the routine assessment of the patients participating in the Programma2000 and, more specifically, of those enrolled from June 1999 to September 2009. The institutional review board (IRB) approved the protocol of the study and it conforms to the provisions of the Declaration of Helsinki in 1995 (as revised in Tokyo 2004). All patients gave their informed consent. The sample included 169 patients from a catchment area of approximately 200,000 inhabitants.

2.1. Assessment and diagnosis

This study used the following standardized assessment instruments: (i) a socio-demographic form; (ii) the Early Recognition Inventory Retrospective Assessment of Symptoms checklist (ERIraos-CL), a 17-item screening checklist intended to select the persons needing a more in-depth assessment (Häfner et al., 1992); (iii) the Health of the Nation Outcome Scale (HoNOS), to assess psychopathology and disability: it includes 12 five-point items to evaluate clinical and social functioning over the prior two weeks (Wing et al., 1998; Preti et al., 2012); (iv) the 24-item Brief Psychiatric Rating Scale (BPRS), to assess general psychopathology (Overall and Gorham, 1962; Roncone et al., 1999); and (v) the Global Assessment of Functioning (GAF) (Moos et al., 2000).

Patients were included in Programma2000 when they were between 17 and 30 years of age, and were referred to Programma2000 after a first contact with any public mental health service of the catchment area for a first episode of psychosis (i.e. their DUP had to be lower than 24 months), or for suspected psychosis. Referral sources were mental-health professionals and associated surgeries, family physicians, or direct family referrals in response to awareness campaigns; self-referral, too, was allowed.

The main criterion for the inclusion of a first episode of psychosis (FEP) was a diagnosis of schizophrenia or related syndromes (F20-29 in ICD-10) according to the ICD-10 (WHO, 1992).

Referred UHR patients were initially screened on the ERIraos-CL: to be enrolled in treatment as UHR, patients must have scored ≥ 12, the threshold score that better defined patients at risk of transition in the German Schizophrenia Network study (Maurer et al., 2006). Patients screened positive on the ERIraos-CL were further evaluated and enrolled when they met one of these PACE operational criteria for UHR: (1) Attenuated Positive Prodromal Syndrome; or (2) Brief, limited, and intermittent psychotic syndrome; or (3) familial genetic risk or Schizotypal Personality Disorder and evidence of deterioration in functioning in the last year, i.e. they showed a decrease of 30% on the GAF with respect to the estimated premorbid functioning (Yung et al., 1996; Phillips et al., 2007). A past or present diagnosis of psychosis in the spectrum of schizophrenia was a mandatory exclusion criterion for UHR diagnosis.

In both FEP and UHR patients, affective psychosis (bipolar disorder, or unipolar disorder with psychotic features) was an exclusion criterion, as was a co-morbid persistent substance-use dependent disorder, while substance use/abuse without dependence was not.

Additional information was collected during the interview of the patient and of at least one key informant (a close relative, and preferably a parent).

A family history of psychosis was defined as:

- any first/second degree relative having received a diagnosis of schizophrenia or a related syndrome (F20-29 in ICD-10; conditions were individually listed);
- or any first/second degree relative having received two or more prescriptions of antipsychotic drugs (drugs were listed) for a condition with hallucinations and/or delusion;
- or any first-second degree relative having been hospitalized in a psychiatric unit twice or more for a condition with hallucinations and/or delusion.

Any positive reply was counted as evidence of a family history of psychosis; for those who were hospitalized or received a prescription of antipsychotic drugs at an outpatient public service, records were checked to confirm the diagnosis. Those cases showing, at the records check, a diagnosis of affective psychosis or bipolar disorder were not counted as positive cases for family history of psychosis.

Duration of untreated illness (DUI) and DUP were both measured as the time elapsed from the onset of key symptoms (anxiety, depression or social withdrawal for DUI, hallucinations, delusions or bizarre behavior for DUP) to the start of treatment (pharmacotherapy or psychotherapy) prescribed by a psychiatrist; DUP was measured in days, DUI in months.

2.2. Obstetric complications

Obstetric complications were defined as any somatic complication occurring during pregnancy, with some potential direct relevance to the physical wellbeing of the offspring. Patients' mothers were asked whether they suffered from any obstetric complication, as defined above. The interview proceeded step by step: first the mother was asked whether something happened during the pregnancy of the patient or at his/her birth; in case of positive reply, a list of obstetric complications was showed to the mother, asking whether any of them occurred during pregnancy of the patient or at his/her birth; explanations were given in case of uncertainty or poor understanding. Patients' mothers were specifically asked whether they had suffered from any of the following events during their pregnancy: Rh or other blood incompatibility; maternal hypertension, diabetes or infection; bleeding; pre-eclampsia; placenta abruption; cord prolapse; breech delivery; foetopelvic disproportion; traumatic delivery; twin birth; pre-term birth; low birthweight (<2500 g at birth); small size for gestational age (2 S.D. below the mean Italian birth weight curve); severe fetal distress/asphyxia; Apgar score below 7 at 5 min and/or postnatal asphyxia; postnatal seizures; life-threatening viral infection of the offspring.

The enlisted conditions were individually associated to a greater risk of receiving the diagnosis of schizophrenia in adulthood for the offspring who suffered them (McNeil et al., 1994; Cantor-Graae et al., 1997). Any positive reply on the query was counted as evidence of OCs. Data were considered globally; therefore, the patients whose mothers gave one or more positive replies on the enlisted conditions were counted as cases with OCs; those whose mother denied the occurrence of any enlisted condition were considered cases without OCs. Information on maternal age and parity was not recorded; information on the education level or psychiatric wellbeing of the mothers was not used in this study, since we were not allowed to by the IRB out of privacy reasons.

2.3. Criteria for outcome

Data on outcome 1 year after the initial assessment were available for a subgroup of patients. According to the Remission in Schizophrenia Working Group (RSWG), remission for the FEP group was defined as a score of mild ($=3$) or lower on all seven items of BPRS considered representative of the core symptoms of psychosis: grandiosity, suspiciousness, unusual thought content, hallucinatory behavior, conceptual disorganization, mannerism/posturing, blunted affect (Andreasen et al., 2005; Lasser et al., 2007).

Transition to psychosis in UHR patients was defined as any score higher than mild (i.e., ≥ 4) on the BPRS items representative of the core symptoms of psychosis, as above, for more than 1 month, or as a formal diagnosis of schizophrenia according to the ICD-10 criteria.

2.4. Statistics

Data were analyzed with the Statistical Package for Social Science (SPSS) for Windows (Chicago, Illinois 60606, USA), version 13.

All tests were two-tailed, threshold of significance was set at $p=0.05$. Categorical data were analyzed in inter-group comparisons with χ^2, or Fisher's exact test, when appropriate ($N<5$ in any cell in contingency tables). The t-test was used for continuous variables; the Mann–Whitney test was used to compare the ordinal variables. For statistical purposes, two continuous variables (age and DUP) were dichotomized. Age was split into two groups: 17–20 years old, and 21–30; the cut-off of 20 produced a 30%–70% splitting of the group, with those in the younger group expected to have a higher incidence of OCs. As for the DUP, cut-off was set at 30 days, since this limit defines an acute presentation of the symptoms, with 42% of the FEP sample classified in this group.

A multiple logistic regression analysis on OCs (method: backward stepwise, likelihood ratio) was applied to the whole sample ($n=169$), taking into account sex, age, diagnosis and family history of psychosis to identify the main effects of the variables potentially associated to OCs.

3. Results

The study included 86 FEP and 83 UHR patients. Both samples had a larger preponderance of male patients; 15% of patients had a first/second degree relative diagnosed with psychosis. There was a slight excess of male patients in the FEP group compared to the UHR group, but no differences in age, educational level, married status, and family history of psychosis (Table 1).

As expected on the basis of classification, FEP patients were more severe than UHR patients, and scored higher on the ERIraos, the HoNOS, and the BPRS, and lower on the GAF.

3.1. Obstetric complications

A history of OCs was reported in 20 (23%) FEP cases and 21 (25%) UHR cases: $\chi^2=0.9$, d.f.$=1$, $p=0.75$.

In FEP patients, family history of psychosis was statistically related to the occurrence of OCs; the same trend was observed in UHR patients, albeit not significantly (Table 2).

Table 1
Baseline characteristics of patients enrolled in Programma2000 (data refer to individuals in treatment until September 2009).

All data: no. (%) or mean (S.D.)	First-episode psychosis $N=86$	Ultra high risk $N=83$	Statistics
Age at entry	22.5 (3.8)	22.3 (3.6)	$t=-0.51$, d.f.$=167$, $p=0.61$
Gender (no., % of males)	$N=70$ (81%)	$N=57$ (69%)	$\chi^2=3.01$, d.f.$=1$, $p=0.08$
Age of males	22.3 (3.7)	22.0 (3.7)	
Age of females	23.4 (4.3)	22.7 (3.5)	
Education			
College graduate or higher	6 (7%)	4 (5%)	$\chi^2=0.66$, d.f.$=2$, $p=0.72$
High school diploma	38 (44%)	41 (49%)	
Lower than high school diploma	42 (49%)	38 (46%)	
Marital status			
Unmarried	84 (98%)	82 (99%)	$\chi^2=0.88$, d.f.$=2$, $p=0.64$
Married	1 (1%)	1 (1%)	
Separated/divorced	1 (1%)	0 (0%)	
Nationality			
Italian	80 (93%)	76 (92%)	$\chi^2=0.14$, d.f.$=2$, $p=0.93$
European non Italian	1 (1%)	1 (1%)	
Non European	5 (6%)	6 (7%)	
Family psychiatric history			
First/second degree relative with psychosis	16 (19%)	9 (11%)	$\chi^2=1.45$, d.f.$=1$, $p=0.23$
Duration of untreated psychosis (days)	172.7 (222.3)	–	
Duration of untreated illness (months)	29.6 (20.8)	31.0 (21.9)	M–W: $z=-0.43$, $p=0.66$
Clinical and functional characteristics at enrollment			
ERIraos-CL	23.3 (8.3)	18.7 (8.0)	M–W: $z=-5.36$, $p=0.0001$
HoNOS, total score	14.9 (6.7)	12.9 (5.4)	M–W: $z=-2.32$, $p=0.020$
BPRS, total score	52.6 (16.9)	44.7 (11.4)	M–W: $z=-2.89$, $p=0.004$
GAF	43.9 (9.1)	53.2 (10.0)	M–W: $z=-5.91$, $p=0.0001$

M–W=Mann–Whitney U test.

Table 2
Obstetric complications (OCs) in the sample, by diagnosis.

	First-episode psychosis $N=86$		Statistics	Ultra high risk $N=83$		Statistics
	N	%		*N*	%	
OCs by family history of psychosis						
Family history of psychosis	7	44%	$\chi^2=4.62$, d.f.$=1$, $p=0.03$	4	44%	$\chi^2=1.95$, d.f.$=1$, $p=0.16$
No family history of psychosis	13	18%		17	23%	
OCs by sex						
Males	18	26%	$\chi^2=0.64$, d.f.$=1$, $p=0.42$	15	26%	$\chi^2=0.09$, d.f.$=1$, $p=0.75$
Females	2	12%		6	23%	
OCs by age						
17-20	8	27%	$\chi^2=0.08$, d.f.$=1$, $p=0.78$	12	39%	$\chi^2=4.49$, d.f.$=1$, $p=0.03$
21-30	12	21%		9	17%	
OCs by DUP						
DUP < 30 days	7	19%	$\chi^2=0.73$, d.f.$=1$, $p=0.38$			
DUP > 30 days	13	26%				

Table 3
Multiple logistic regression analysis of the factors associated to obstetric complications in the sample ($N=169$).

All data *n* (%)	**OCs by indicator**	**Wald χ^2**	**d.f.**	***p***	**OR (95% CI)**
Sex (females)	8 (19%)	0.502	1	0.479	0.72 (0.29–1.77)
Age (21 years old and older)	21 (20%)	3.738	1	0.053	0.48 (0.23–1.01)
Diagnosis (FEP)	20 (23%)	0.4	1	0.527	0.79 (0.38–1.64)
Family history of psychosis (Yes)	11 (44%)	5.904	1	0.015	**3.05 (1.24–7.53)**

Method: backward stepwise, likelihood ratio (entry: $p=0.05$; removal: $p=0.10$); each equation controlled for sex of participants (females versus males), age (17–20 years old versus 21 years old and older), diagnosis (FEP versus UHR) and family history of psychosis (Yes versus No).

In FEP patients, OCs tended to be (not significantly) more frequent in males and in those with DUP exceeding 30 days. In UHR patients, sex was not related to a history of OCs, but age was: patients younger than 21 were more likely to have a history of OCs than older patients. A history of OCs was not related to severity at enrollment in patients with FEP or in those with UHR (data available on request).

The multiple logistic regression analysis on OCs applied to the whole sample ($N=169$) showed that family history of psychosis and younger age, marginally, were related to OCs (Cox & Snell $R^2=0.053$; Nagelkerke $R^2=0.080$; $\chi^2=9.23$, $p<0.01$) (Table 3).

3.2. Obstetric complications and outcome

Data on outcome at 1 year were available for 59 FEP patients (13 had OCs) and 61 UHR patients (12 had OCs). The reasons for missing data at the 12-month follow-up were: the first year of treatment being not completed yet, or raters having not reported the rating in the report (there were no dropouts in the first year of treatment). Patients with available data at 12-month follow-up did not differ from patients whose data were missing on the BPRS, HoNOS or GAF as measured at initial assessment (Mann–Whitney *U* test $p>0.05$ in all analyses).

In FEP patients with available data at 1-year follow-up, OCs were not related to failure to attain remission at 1 year: cases with OCs were 5 out of 19 (26%) among those who did not attain remission, versus 8 out of 40 (20%) among those who attained remission (Fisher's exact test $p=0.73$).

In the UHR sample, six patients converted to psychosis according to the predetermined criteria; two of them received a formal ICD-10 diagnosis of schizophrenia. Among UHR patients that converted to psychosis, two had a history of OCs (33%); among those that did not convert to psychosis, 10 out of 55 had a history of OCs (18%); the difference was not statistically significant (Fisher's exact test $p=0.58$). As far as the two cases that received a diagnosis of schizophrenia were concerned, one had a history of obstetric complications and one had no history of obstetric complications.

4. Discussion

This study found no significant difference in the incidence of OCs between FEP and UHR patients. However, a family history of psychosis within the spectrum of schizophrenia was related to the occurrence of OCs in FEP and, albeit not significantly, in UHR patients.

4.1. Links of sex and age with OCs in FEP and UHR patients

No statistically significant differences were found in the incidence of OCs by sex in both the FEP and the UHR sample. In UHR patients, but not in FEP patients, younger patients were more likely to have a history of OCs. In some but not all past studies, a history of OCs was found to be associated to earlier onset of psychosis (O'Callaghan et al., 1992; Verdoux et al., 1997; Kelly et al., 2004). The same effect could be operating on the onset of attenuated or transient psychotic symptoms. Sample size prevented a real test of the hypothesis that conversion to psychosis in UHR is more likely in those who had suffered OCs. Indeed, the study is underpowered to test the relationship between some variables and the occurrence of OCs. This limitation should be taken into account when considering some of the negative findings.

4.2. OCs and outcome at 1-year in FEP and UHR cases

No statistically significant link was found with the indicators of severity or outcome at 1-year follow-up. FEP patients with a history of OCs tended to have a longer DUP than patients without OCs. In past studies, an insidious onset of psychosis was associated to longer DUP (Thomas and Nandhra, 2009), so OCs might

be a factor involved in the insidious onset of psychosis. Larger samples than ours are necessary to test the hypothesis that DUP is a factor involved in the relationship between a history of OCs and brief/medium-term outcome in psychosis.

4.3. Family history of psychosis and the occurrence of OCs

The most important finding of the study was that in FEP patients, and marginally in UHR patients, those with a family history of psychosis were more likely to have had a history of OCs than those without a family history of psychosis. Family history of psychosis remained a predictor of OCs in the whole sample, even taking into account sex, age and diagnosis. Overall, this finding is congruent with the hypothesis that OCs interact with genetic vulnerability to increase the risk of the disorder (Mueser and McGurk, 2004; Mittal et al., 2008; Preti and Wilson, 2011). Indeed, one study reported some indicator of abnormal or delayed neurodevelopment (e.g. small head circumference at birth) to be associated with a positive family history in schizophrenia (Kunugi et al., 1996); another study found that maternal prenatal exposure to infections increased the risk of schizophrenia in those who had a family history of psychosis compared to those who did not (Clarke et al., 2009). More recent studies reported an interaction between severe OCs and genes implied in the reaction to hypoxia events in influencing the risk of schizophrenia (Nicodemus et al., 2008). Links between schizophrenia candidate genes and hypoxia regulation or vascular expression have been confirmed in genome-wide association studies (Schmidt-Kastner et al., 2012).

However, other studies found that the specific familial morbid risk of schizophrenia and related psychoses was not associated with OCs (Cantor-Graae et al., 1994; Marcelis et al., 1998). Conversely, familial liability for schizophrenia was related to early onset and very early onset schizophrenia independently from a history of OCs (Margari et al., 2011). In another study, birth complications were predictors for earlier onset of schizophrenia in patients with non-familial schizophrenia (Scherr et al., 2011). The links between family history of psychosis and OCs could be indirect. There is some evidence that women with psychotic disorders are exposed to a higher risk of OCs (Howard, 2005; Ellman et al., 2007). This enhanced risk of OCs is supposed to depend on poor attendance to obstetric care and/or health-damaging behaviors (e.g., smoking during pregnancy). Families with a relative diagnosed with psychosis suffer a high burden of care, and this burden of care is often on charge of women, who might be overwhelmed by this burden to the point of neglecting medical advises. In so far, this is mere speculation, since no study had specifically investigated the topic.

4.4. Limitations of the study

Before extrapolating any conclusion from the results of this study, its limitations should be taken into account. The first limitation is the use of a global measure of OCs based on maternal interview. Maternal recall of obstetric complications has been questioned as a reliable source of information (Cantor-Graae et al., 1998; McIntosh et al., 2002), but the studies that compared maternal recall with hospital records found evidence of accuracy in OC reporting (O'Callaghan et al., 1990). In general, the accuracy of maternal recall about obstetric complications varied depending on the nature of the complications examined, with greater accuracy for birth events (Sou et al., 2006). When bias occurred, it produced the reporting of fewer complications than indicated in the obstetric records, with no evidence of positive recall bias (Buka et al., 2000). Recent studies confirmed that the mothers of patients diagnosed with schizophrenia show valid and well-preserved long-term recall of OCs and of the birth events related to their offspring; several complications of pregnancy and delivery were accurately recalled by the mother decades after they had occurred (Walshe et al., 2011). Due to study constraints, raters could not take note of any single occurrence of OCs reported by the patients' mothers. As a consequence, OCs were classified in a binary yes/no format, and no record was taken on the specific typology of the OCs or of the multiplicity of them, a potential measure of greater severity. Nevertheless, all the OCs considered in this study were reported in the past as being associated to a higher chance of the offspring's being diagnosed with schizophrenia in adulthood (McNeil et al., 1994; Cantor-Graae et al., 1997), and we are confident that the cases classified as positive for OCs had actually experienced them.

A second limitation is the lack of a control group including putatively healthy people. Therefore, there is no certainty that the 23–25% incidence of OCs recorded in the sample is really higher than the incidence that could be observed in people without a FEP or UHR diagnosis. However, in a study done in north-east Italy using the same list of severe OCs to define the risk of potential harm to the physical wellbeing of the offspring, a global OC incidence of 9% was found in the obstetric records of putatively healthy people, i.e. people who had no contact with the psychiatric services of the area where the study was done (Preti et al., 2000). It should be noted that the study by Preti et al. (2000) relied on birth records rather than on maternal recall to identify severe OCs. Moreover, the percentage of severe OCs retrieved in the birth records in the Preti et al. (2000) paper was 34%, a higher rate than the one derived from maternal recall in this study (23–25%). Improvement in obstetric care over time could be a factor contributing to this difference; however, this difference could be also an indication of maternal under-reporting of OCs in the current study, as signaled in the past (Cantor-Graae et al., 1998; Buka et al., 2000).

5. Conclusions

In conclusion the findings of this study, like those of a past study (Ballon et al., 2008), suggest that OCs cannot be totally discounted as a factor involved in the outcome of UHR people. The incidence of OCs in UHR samples is similar to the incidence observed in samples of patients diagnosed with schizophrenia-spectrum psychosis, a group known to have been more exposed to OCs (Cannon et al., 2002); in UHR patients the occurrence of OCs related to younger age, a finding reminiscent of the association of OCs with earlier onset of psychosis (O'Callaghan et al., 1992; Verdoux et al., 1997). However, we must acknowledge that the findings are of decreased value because no comparison to healthy controls has been performed.

Nevertheless, we feel, as suggested in the past by Warner (2001), that interventions aimed at decreasing the occurrence of OCs might impact on the incidence of psychosis, safely and at low cost. More specifically, women with mental disorders should be followed with care during pregnancy, since they are exposed to a greater risk of OCs (Howard, 2005; Ellman et al., 2007). Early detection of those in need of care, and not merely in the psychiatric setting, is an option for primary prevention of schizophrenia and its related psychoses.

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