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ABSTRACT

The impact of stressful experiences during gestation or early life, leading to increased psychiatric disorders susceptibility, is currently well described in literature, however, few data are available on the association between obstetrical complications and later development of specific diagnoses or clinical features (e.g. psychotic symptoms). Aim of the present paper was to evaluate obstetrical complications frequency in different psychiatric diagnoses and their association with clinical features. Three hundred and eighty-eight patients with a diagnosis of schizophrenia, bipolar disorder or major depressive disorder were compared in terms of clinical presentation according to the presence, type and severity of obstetrical complications. Seventeen percent of the total sample (N=65) had history of at least one obstetrical complication. Patients with a history of at least one obstetrical complication result in an earlier age of onset (F=3.93, p=0.04) and a current higher GAF score (F=6.46, p=0.01). Lewis-Murray scale score was directly correlated with GAF scores (t=2.9, p=0.004) and inversely correlated with age at onset (t=-2.77, p=0.006). Obstetrical complications are frequently registered in patients with schizophrenia or mood disorders. In our sample, they appear to have an anticipatory effect on illness onset, but they seem not to be associated with a specific psychiatric diagnosis.

Key words: Obstetrical complications, Schizophrenia, Mood Disorders

1. Introduction

Obstetric complications can have significant implications for mental health in adulthood and have been associated with increased risk of psychiatric disorders (Freed et al., 2014).

With regard to schizophrenia, obstetric complications, particularly those associated with hypoxia, appear to be associated with an increased risk to develop psychosis (Cannon et al., 2002). Early hypoxia would cause an abnormal brain development during childhood (Haukvik et al., 2012), and, in support of this hypothesis, hippocampus, basal ganglia and amygdala atrophy have been found more frequently in schizophrenic patients with obstetric complications than in patients without perinatal insults (Murray et al., 2004; Morales et al., 2011). Moreover poor treatment response has been reported in schizophrenia patients with a history of obstetric complications (Alvir et al., 1999).

The role of obstetric complications in the etiology of bipolar disorder is controversial: a systematic review concluded that there is no robust evidence that exposure to obstetric complications increases the risk of developing bipolar disorder (Scott et al., 2006). Obstetric complications appear to be more related to specific bipolar subtypes such as the early-onset (Guth et al., 1993) or psychotic ones (Hultman et al., 1999). Alternatively, only specific obstetric complications are associated with an increased risk of future bipolar disorder: a recent paper found that children delivered by planned caesarean section had a 2.5-fold increased risk of bipolar disorder (Chudal et al., 2014), while another paper found a 2.7-fold increased risk in case of preterm birth (Nosarti et al., 2012).

Data about the role of obstetric complications in major depressive disorder are even more scanty than in bipolar disorder (Schmitt et al., 2014). Three independent studies found that preterm birth was associated with a higher risk of a depressive disorder in adolescence (Patton et al., 2004) or adulthood (Räikkönen et al., 2007; Nosarti et al., 2012).

From a patho-physiological perspective, it is unclear whether obstetric complications are injuries that alter brain development or, vice versa, they are an early sign of a predisposition to psychiatric disorders (Walder et al., 2014). In addition, it is not determined whether obstetric complications are associated with a specific psychiatric diagnosis or are generally a risk factor for psychiatric symptoms in adulthood (Lukkari et al., 2012).

In light of previously mentioned data, the main purpose of this study was to compare patients according to the presence of at least one obstetrical complication in terms of demographic and clinical variables. Secondary objectives were:

- to verify if specific obstetrical complications (e.g. delivery by forceps) were more frequently associated with peculiar clinical features,

- to verify if obstetrical complications severity was related to global functioning, age at onset and duration of illness,

- to compare different diagnostic groups (including patients with a history of psychotic symptoms) in terms of obstetrical complication severity.

2. Methods

As regards the calculation of the sample size, we considered that the population afferent to our department with schizophrenia or mood disorders corresponds to approximately 2000 patients. We then assumed that a difference of 5 in continuous variables (e.g. age at onset) between patients with a history of obstetric complications and those without would be significant. In this case for a statistical significance < 0.05, a sample of 322 patients may be considered powerful.

Three hundred and eighty-eight patients were enrolled from those followed up by the Department of Psychiatry of University of Milan, treated in the Inpatient Clinic between January 2010 and March 2014. Data collection was carried out from April 2014 to December 2014. We included patients that received a diagnosis of Schizophrenia (SKZ), Bipolar Disorder (BD) type 1 or 2, Major Depressive Disorder (MDD) according to DSM-5 criteria (The Diagnostic and

Statistical Manual of Mental Disorders, American Psychiatry Association, 2013). In electronic clinical charts, diagnoses were made according to DSM-IV-TR (The Diagnostic and Statistical Manual of Mental Disorders–Text Revision) (2010-June 2013) and then DSM-5 and in PSICHE database according to ICD-9 (International Classification of Diseases). No patients have been excluded according to retrospective revision of diagnosis according to DSM-5.

Diagnoses were made by senior expert psychiatrists who regularly follow patients included in the study.

Exclusion criteria were the following:

1) patients whose clinical information was incomplete;

2) patients with a diagnosis of dementia, mental retardation or other medical conditions (e.g. hypothyroidism) associated with psychiatric symptoms;

3) patients that were hospitalized at the time of recruitment or had an acute exacerbation of symptoms as defined by a Positive and Negative Syndrome Scale (PANSS) score > 50 (Leucht et al., 2005), a Young Mania Rating Scale (YMRS) score > 10 or Hamilton Depression Rating Scale (HAM-D) score > 8 (Vieta and Moralla, 2010). This exclusion criterion is justified by the fact that acute symptoms would have created a bias in the assessment of GAF.

Following these criteria, 15% of the initial screened patients were excluded.

Clinical information were extrapolated through a retrospective review of electronic clinical charts (primary and main information source), Lombardy database (PSICHE) (42% of cases) and, if necessary, through clinical interviews with patients and their relatives (2.6% of cases). Collected data included the following demographic and clinical variables: age, gender, diagnosis, age at onset, lifetime history of psychotic symptoms, duration of illness, Global Assessment of Functioning (GAF) scores (Jones et al., 1995). The presence and severity of obstetrical complications was evaluated by Lewis-Murray scale (Lewis and Murray, 1987).

Descriptive analyses of the total sample were performed. The patients were divided according to the presence of at least one obstetrical complication and the groups were compared by χ^2 tests for

dichotomous variables (gender, lifetime history of psychotic symptoms, and diagnosis). The same groups were compared for continuous variables (age, age at onset, GAF scores and duration of illness) by multivariate analyses of variance (MANOVAs). The sample was then divided according to the most frequent obstetrical complications (> 1%) (labor > 36 hours, complicated twin birth, gestational age < 37 weeks or > 42 weeks, complicated caesarian delivery, forceps, birth weight < 2000g, incubator, gross physical anomaly) and the groups were compared for the same variables by using the same statistical methods (χ^2 tests for dichotomous variables and MANOVAs for continuous variables). A linear regression analysis was then performed to see if the severity of obstetrical complications (Lewis-Murray scale total score) was related to GAF scores, age at onset or duration of illness. Finally one-way analyses of variance were performed to compare Lewis-Murray scale total scores (severity of obstetrical complications) between groups divided according to type of diagnosis and lifetime history of psychotic symptoms.

The level of statistical significance was set at 0.05. Statistical Package for Social Sciences (SPSS) for Windows (version 21.0) was used for statistical analyses.

3. Results

The final sample included 388 patients: 202 males (52.1%) and 186 females (47.9%). Descriptive analyses are reported in Table 1. Seventeen percent of the total sample (N=65) had history of at least one obstetrical complication. The frequency of each obstetrical complication according to Lewis-Murray scale is reported in Table 2.

Patients, divided according to the history of at least one obstetrical complication, resulted to be homogenous in terms of gender (χ^2=0.74, df=1, p=0.42, phi=0.04), diagnosis (χ^2=5.97, df=3, p=0.11, phi=0.12) and lifetime history of psychotic symptoms (χ^2=0.02, df=1, p=1.00, phi=0.01). With regard to continuous variables, the MANOVA model resulted to be valid (Wilks'test: p<0.001). Patients with a history of at least one obstetrical complication resulted in an earlier age at onset (F=3.93, p=0.048, d=0.27) (Figure 1) and a current higher GAF score (F=6.46, p=0.011,

d=0.35) (Figure 2). In contrast, the groups, divided according to the history of at least one obstetrical complication, did not differ according to the duration of illness (F=0.06, p=0.81, d=0.03).

The analyses performed with the sample divided according to the most frequent obstetrical complications (labor > 36 hours, complicated twin birth, gestational age < 37 weeks or > 42 weeks, complicated caesarian delivery, forceps, birth weight < 2000g, incubator, gross physical anomaly), did not show any statistical significance.

The linear regression showed that Lewis-Murray scale score was directly correlated with GAF scores (t=2.9, p=0.004) (Figure 3) and inversely correlated with age at onset (t=-2.77, p=0.006) (Figure 4). In contrast, no correlation was found between Lewis Murray scale score and duration of illness (t=-0.75, p=0.45).

Finally, Lewis-Murray total scores did not differ between groups divided according to diagnosis (F=0.92, p=0.43) or lifetime history of psychotic symptoms (F=0.61, p=0.65).

4. Discussion

The first result emerging from our study is that 17% of patients suffering from psychotic or mood disorders had a history of obstetrical complications. In our sample, the most common obstetrical complications resulted to be prolonged labor (more than 36 hours) (6.7%), gestational age < 37 weeks or > 42 weeks (7.2%), complicated caesarian delivery (4.4%). Similarly, in another retrospective study, cesarean delivery resulted to be the most common obstetrical complication in patients with subthreshold psychotic symptoms with respect to healthy controls (Kotlicka-Antczak et al., 2014).

The second result of this study is that patients with a history of perinatal insults presented an earlier age at onset and higher GAF scores compared to patients without obstetric complications. Higher GAF scores might be explained by an earlier access to the mental health services (e.g. neuropsychiatry), thus patients have a shorter DUI that has been associated with a better outcome in

the long-term (Altamura et al., 2015). On the other hand, obstetrical complications could have an "anticipatory effect" (possibly determining early presentation of psychiatric disorders in subjects with a predisposition to mental illness), as demonstrated by the earlier age at onset in this group. It seems that obstetrical complication can give an adjunctive vulnerability to develop earlier psychiatric disorders, confirming previous findings outlined in patients with schizophrenia or mood disorders (Guth et al., 1993; Kotlicka-Antczak et al., 2001). In this way, future research could investigate the role of obstetric complications in subjects with high risk of psychosis in terms of their impact on probability and time to transition to a full-blown psychotic disorder

The role of obstetrical complications in the etiology of schizophrenia or bipolar disorder, is currently debated: two independent papers did not find enough evidence of this association respectively in ultra-high risk patients for schizophrenia (Yun et al., 2005) and in schizophrenia patients (Byrne et al., 2000). In contrast, Preti and co-authors demonstrated that schizophrenic patients had significantly more frequently obstetrical complications than healthy subjects (Preti et al., 2000). Other authors indicated that prematurity was modestly associated with the risk to develop schizophrenia (Byrne et al., 2007). In addition, cesarean delivery was found to increase the risk of bipolar disorder in a Finnish sample (Chudal e al., 2014), while Martelon and co-authors did not find significant differences between bipolar patients and healthy controls in terms of obstetrical complications (Martelon et al., 2012).

In the present study, nor specific obstetric complication neither global severity of perinatal insults (Lewis-Murray total scores) were associated with a particular diagnosis or with psychotic symptoms, suggesting that perinatal problems are unspecific "noxa" which contribute to an early presentation of a psychiatric disorder, but not to a certain diagnosis (e.g. schizophrenia vs bipolar disorder). Interestingly, our study seems to support available data on cesarean delivery and subsequent increased risk of psychotic/bipolar disorders (Kotlicka-Antczak et al., 2014; Chudal e al., 2014; Boog 2003). The originality and strength of the present research is represented by the

inclusion of different diagnostic groups with the aim to study the role of obstetrical complications in the etiology of schizophrenia and mood disorders.

Limits of the present study are represented by:

- small sample size, not able to generate the statistical power needed to look at specific obstetric complications;

- retrospective design: the collection of data could have been inaccurate in some cases due to recall bias by parents and/or subjects ;

- more clinical variables should have been taken into account, but in this case a larger sample was needed;

- some variables, such as the psychopharmacological treatment, the presence/absence of social support, the treatment compliance might have influenced GAF scores;

- the use of Lewis-Murray Scale limits the possibility to compare our data with those coming from general population: gynecologists consider obstetric complications not only those which affect future offspring mental health, but also those which impact on general women's health (e.g. puerperal infections) (Thornton et al., 2010)

Future studies should be conducted prospectively in order to collect precise data about mental health of offspring with a history of obstetrical complications and to reduce the risk of developing a psychiatric disorder. As outlined years ago, it could be possible to reduce the risk of schizophrenia in some genetically at-risk individuals by careful prenatal and perinatal monitoring (Warner, 1995). Finally, the inclusion of obstetric complications in multiple risk assessments for psychosis development could enhance our ability to identify those individuals that could benefit of early psychiatric intervention (Mittal 2008a,b; Ballon et al., 2008).

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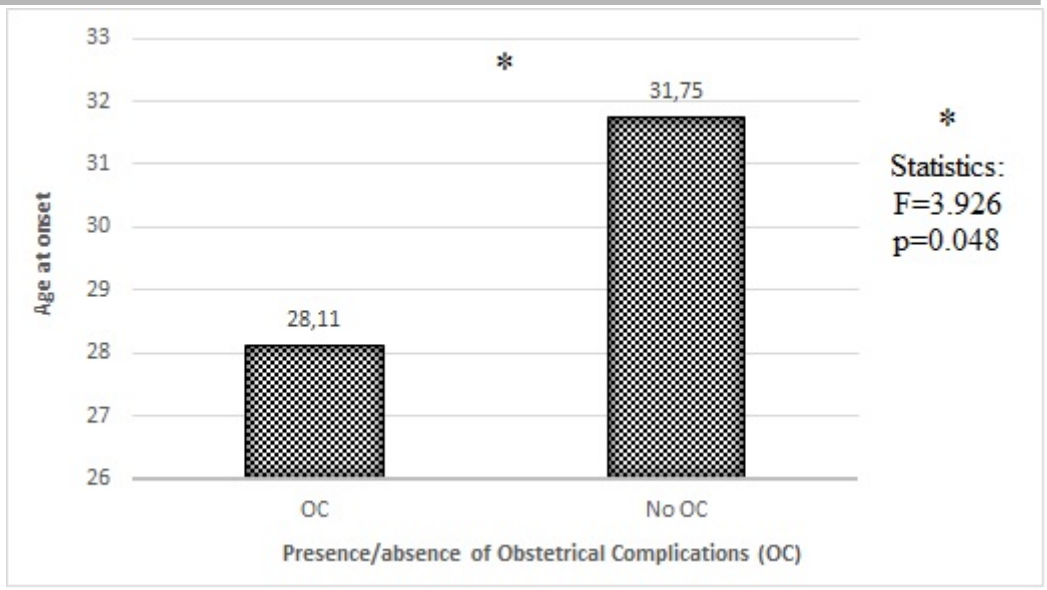
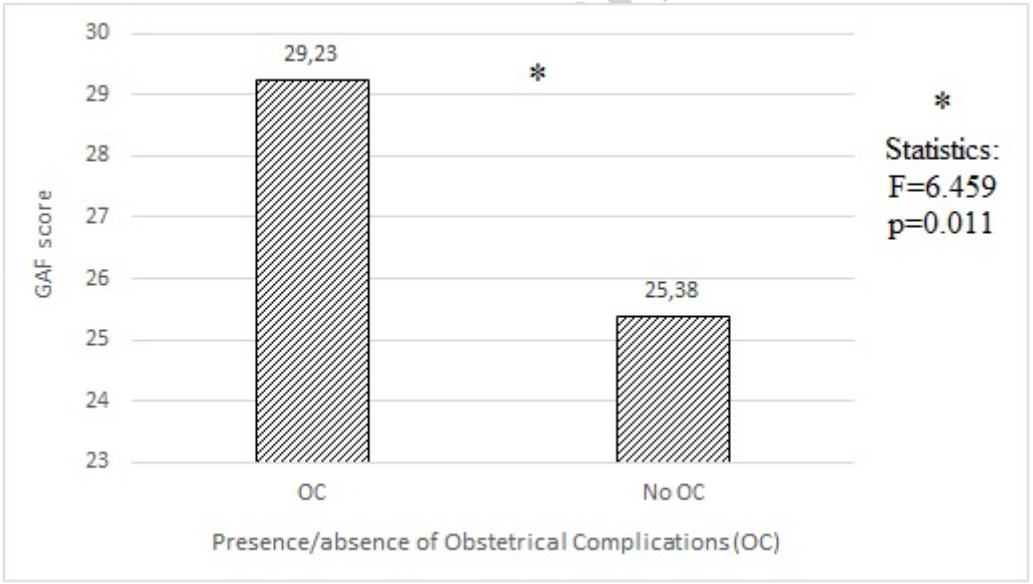
Figure 1. Association between age at onset and presence/absence of obstetrical complications



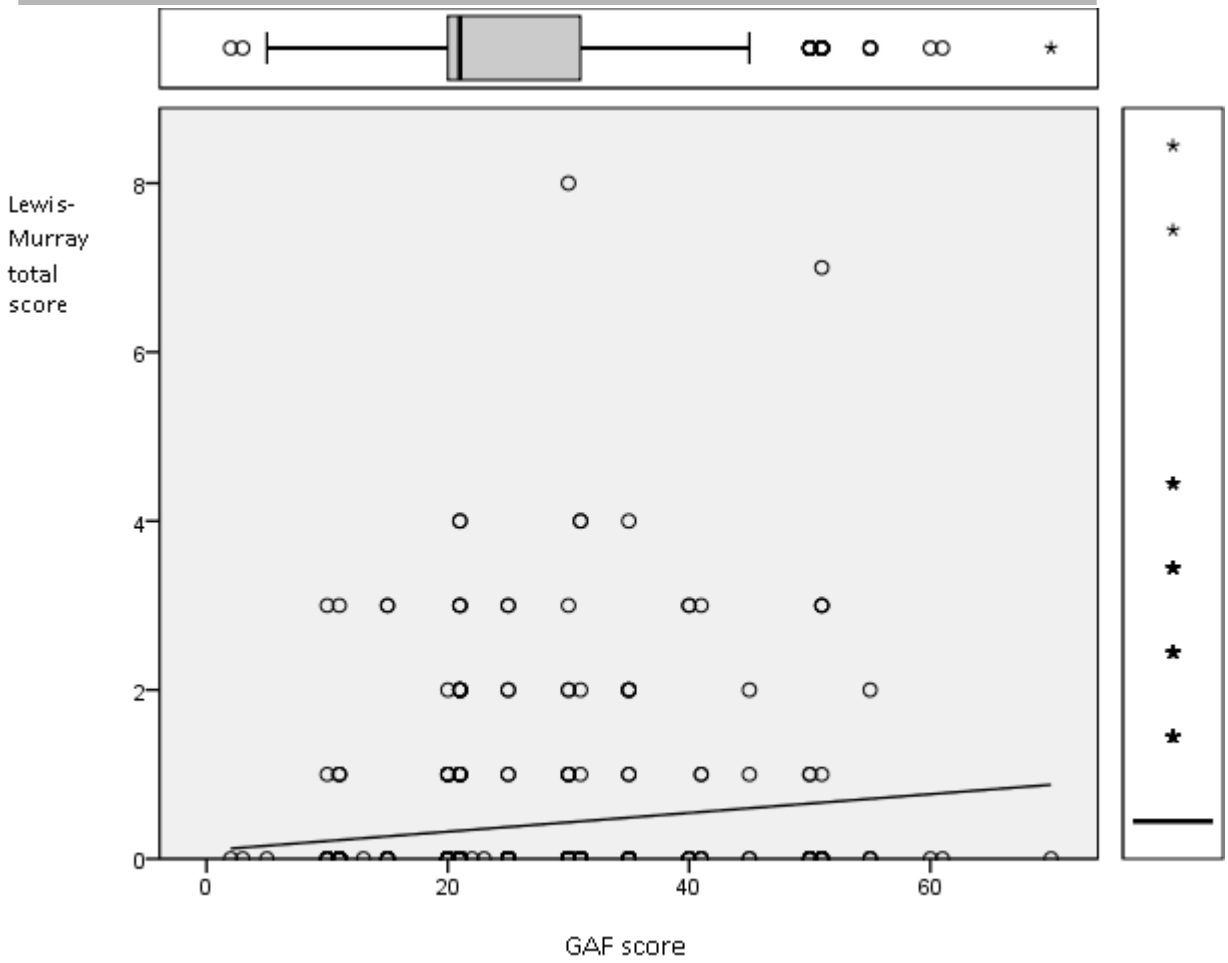
Legend : OC=obstetrical complications

Figure 2. Association between GAF scores and presence/absence of obstetrical complications



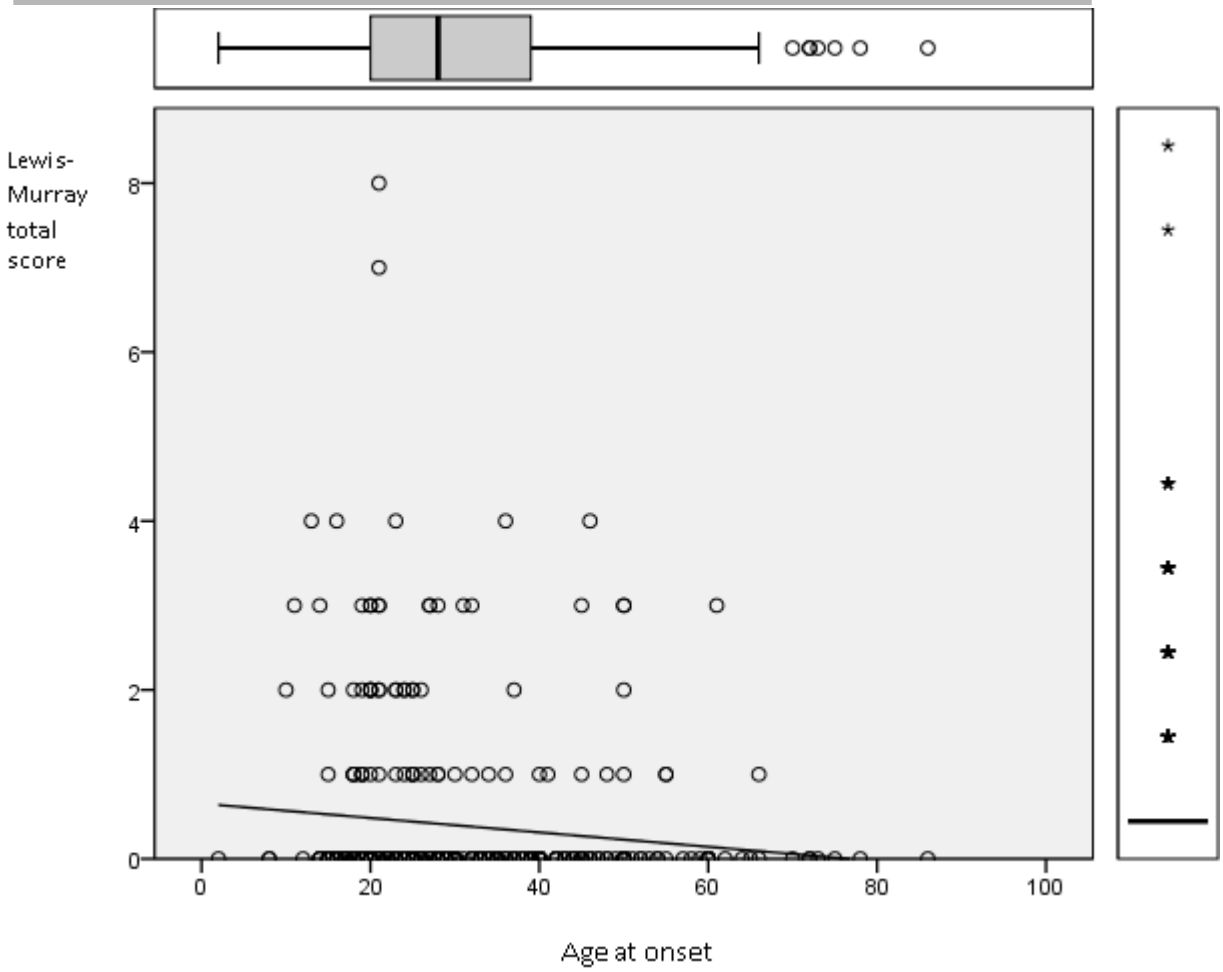
Legend : OC=obstetrical complications

Figure 3. Correlation between GAF scores and total Lewis-Murray scores



Statistics: t=2.9, p=0.004

Figure 4. Correlation between age at onset and total Lewis-Murray scores



Statistics: t=-2.77, p=0.006

Table 1. Demographic and clinical variables of the total sample

Variables		
Gender	Male	202 (52.1%)
	Female	186 (47.9%)
Age	49.45 (± 14.94)	
Diagnosis	Schizophrenia	51 (13.2%)
	BD type 1	245 (63.1%)

	BD type 2	17 (4.4%)
	MDD	75 (19.3%)
Age at onset	31.14 (± 13.57)	
History of psychotic symptoms lifetime	Yes	194 (50%)
	No	194 (50%)
Duration of illness	18.16 (± 14.12)	
Obstetrical complications	Yes	65 (16.8%)
	No	323 (83.2%)
Lewis-Murray total score	0.39 (± 1)	
Other infections during pregnancy (not included in Lewis-Murray scale)	Yes	0 (0%)
	No	388 (100%)
GAF scores	26.03 (± 11.22)	

Legend: BD=Bipolar Disorder; MDD=Major Depressive Disorder; GAF=Global Assessment of Funcitoning

Standard deviations for continuous variables and percentages for dichotomic ones are reported into brackets.

Table 2. Frequency of each obstetrical complication according to Lewis-Murray scale

Obstetrical Complications Antepartum			RD
Rubella or siphilis	Yes	0	0
	No	388 (100%)	
Rhesus incompatibility	Yes	0	0
	No	388 (100%)	
Preeclampsia	Yes	1 (0.3%)	0.02
	No	387 (99.7%)	

Antepartum hemorrage or threatened abortion	Yes No	0 388 (100%)	0
Obstetrical Complications Intrapartum			
Premature rupture of membranes > 24 hours	Yes No	2 (0.5%) 386 (99.5%)	0.03
Labor > 36 hours or < 3 hours	Yes No	26 (6.7%) 362 (93.3%)	0.4
Twin birth, complicated	Yes No	5 (1.3%) 383 (98.7%)	0.08
Cord collapse	Yes No	2 (0.5%) 386 (99.5%)	0.03
Gestational age < 37 weeks or > 42 weeks	Yes No	28 (7.2%) 360 (92.8%)	0.43
Cesarean complicated or emergency	Yes No	17 (4.4%) 371 (95.6%)	0.26
Breech or abnormal presentation	Yes No	2 (0.5%) 386 (99.5%)	0.03
High or « difficult » forceps	Yes No	14 (3.6%) 374 (96.4%)	0.22
Birthweight < 2000 g	Yes No	4 (1%) 384 (99%)	0.06
Incubator	Yes No	10 (2.6%) 378 (97.4%)	0.15
Gross physical anomaly	Yes No	7 (1.8%) 381 (98.2%)	0.11

Legend: bolded=most frequent obstetrical complications in our sample (> 1%) ; RD=risk difference between patients with obstetrical complications versus patients without these complications

Highlights

- The association between obstetrical complications and clinical features in schizophrenia/mood disorders has not been fully investigated yet
- Patients with a history of at least one obstetrical complication result to have an earlier age at onset

- Obstetrical complications do not appear to be associated with specific diagnoses or psychotic symptoms
- Obstetrical complications appear to be unspecific harmful factors having an anticipatory effect in patients with schizophrenia or a mood disorder