Our study is still underway and whether these observations have any impact on hard clinical outcomes or not should be investigated with a great number of patients and with a long-term follow-up.

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Difficulties in delivery and depressive symptomatology in schizophrenia☆

Dificultades en el parto y sintomatología depresiva en la esquizofrenia

Schizophrenia is a complex disorder characterized by a wide range of symptomatology including positive (e.g. delusions, hallucinations) and negative (e.g. apathy, avolition) symptoms associated with increased medical morbidity and early mortality.[1] The current literature describes its origins as a gene plus environmental disorder, in which obstetric complications are a major risk factor.[2] However, obstetric complications are typically quantified as a homogeneous entity (i.e. a dichotomous variable regarding its presence or absence). Our previous study highlighted its heterogeneity,[3] suggesting that different patterns of obstetric complications were associated with different birth weights, an outcome with further cognitive[4] and metabolic implications.[5] In between those, difficulties in delivery have been correlated a higher prevalence of psychosis in the offspring[6] suggesting the activation of specific genes involved in neurovascular function or regulated by hypoxia.[7]

We aimed to evaluate if different patterns of obstetric complications are associated with a specific clinical pattern in stable patients diagnosed with schizophrenia.

Ninety-eight patients were included from a multi-center cross-sectional study of negative symptoms in schizophrenia. The Lewis-Murray scale was used to evaluate obstetric complications and stratified our sample into three subgroups as suggested by Cannon et al.[2] Two groups were characterized by complications during the gestational period, while the other group was characterized by difficulties in delivery (i.e. premature rupture of membranes or pre-labor rupture of membranes; duration of delivery over 36 h or below 3 h; prolapsed umbilical cord; complicated cesarean; abnormal fetal presentation; use of forceps; and incubation for over 4 weeks).

Patients were clinically evaluated with the Positive and Negative Syndrome Scale (PANSS), the Brief Negative Symptom Scale (BNSS) and the Calgary Depression Scale for Schizophrenia (CDSS). They were compared with non-paired Student's t-test, Mann-Whitney U Test or X^2 for comparison of proportions with SPSS v23.0.

All local research ethic committees approved the study.

Patients were either grouped into having difficulties in delivery (N = 26) or not (N = 72). We found no significant differences in general demographic and clinical variables (see Table 1). However, significant differences were found in three specific items from the general psychopathology subscale from the PANSS, with significant differences in anxiety: patients with difficulties in delivery (3.1; SD 1.2) and without (2.4; SD 1.0) (p=0.003); guilt feelings: mean in patients with difficulties (2.5; SD 1.4) and without (1.7; SD 1.1) (p=0.003), and unusual thought content: mean in the group with difficulties in delivery (2.3; SD 1.2) and without (1.7; SD 1.1) (p=0.003). We also found significant differences in two specific items from the CDSS: in guilty ideas of reference: mean in patients with difficulties (0.5; SD 0.7) and without (0.2; SD 0.4) (p=0.001), and in pathological guilt: mean in patients with difficulties in delivery (0.6; SD 0.8) and without (0.2; SD 0.4) (p=0.002).

As brain maturation is extremely sensitive to timing during gestation and perinatal period, we included gender as a potential confounding factor. A general linear model analysis was conducted with the significant items as dependent variables, with gender, and the presence of difficulties in delivery (dichotomous variable yes/no) as independent variables. When considering total general psychopathology from PANSS and specifically anxiety, guilt feelings and unusual thought content items, and the total CDSS symptomatology and specifically guilty ideas of reference and pathological guilt

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Table 1 Presence of difficulties in delivery and demographic and clinical characteristics.

	Without difficulties in delivery N = 72	**With difficulties in delivery** N = 26	*p* value
Age (SD)	33.9 (7.9)	33.6 (10.4)	0.880
Gender (%): **Males**	65	62	0.773
Females	35	38	
Antipsychotic dose (SD) (chlorpromazine equivalents)	407.3 (388.4) **(N = 70)**	1340.2 (3717.9) **(N = 23)**	0.167
PANSS - Positive (SD)	11.7 (4.6)	13.0 (4.5)	0.231
PANSS - Negative (SD)	18.3 (5.7)	18.6 (6.0)	0.854
PANSS - Total (SD)	60.3 (15.4)	65.4 (18.2)	0.171
PANSS - General (SD)	30.1 (8.3)	33.9 (10.2)	0.068
BNSS (SD)	26.8 (12.8)	29.7 (15.9)	0.345
CDSS (SD)	2.7 (3.0)	4.8 (5.4)	0.154

SD: standard deviation; **PANSS:** Positive and Negative Syndrome Scale; **BNSS:** Brief Negative Symptom Scale; **CDSS:** Calgary Depression Scale for Schizophrenia.

as the dependent variables, they were significantly associated with the presence of difficulties in delivery (total general psychopathology from the PANSS $p = 0.05$; anxiety $p = 0.002$; guilt feelings $p = 0.003$; unusual thought content $p = 0.025$; total CDSS $p = 0.017$; guilty ideas of reference $p = 0.002$ and pathological guilt $p = 0.002$) after adjusting for Bonferroni correction for multiple comparisons. Gender was significantly associated only in PANSS general psychopathology total score (p=0.011) and in the anxiety item specifically (p=0.026).

Our results confirm that a specific pattern of obstetric complications, such as difficulties in delivery, are associated with more severe clinical symptomatology, mainly depressive, with specific significance in guilt in a sample of clinically-stable outpatients diagnosed with schizophrenia. Of particular interest, following a previous study,[8] the CDSS has been analyzed suggesting two separate factors, depression-hopelessness and guilt,[9] with the last one being positively correlated with the PANSS General Score and interpreted as a cognitive factor, both measures associated with delivery difficulties in our sample. Difficulties in delivery are associated with a higher risk of psychosis based on a gene*environmental model suggesting the importance of hypoxia associated with a problematic labor.[7] Another important consequence of delivery difficulties, cesarean section, is associated with lower cognitive performance.[6] One important limitation is that patients were categorized according to the presence or absence of risk factors grouped into three categories. As such, the presence of those factors did not exclude the presence of other group factors (having obstetric complications in the other two groups studied), so other described events might have affected the results.

Our results highlight that obstetric complications are a heterogeneous entity in the outcome of schizophrenia and so its specification might help understand its complex heterogeneity.[3]

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Cardiogenic shock and multiorgan dysfunction secondary to clozapine☆

Shock cardiogénico y disfunción multiorgánica secundaria a clozapina

Clozapine was the first antipsychotic drug to be defined as atypical due to its particular properties and is currently known for its use in refractory psychosis. It produces minimum extra pyramidal effects but is not, however, exempt from several side effects such agranulocytosis and myocarditis.

We present the case of a 62-year-old woman, an ex-smoker, obese and with a psychiatric history of schizoaffective disorder. She was hospitalized due to psychotic imbalance. She began new treatment there with clozapine, taking a dose of 900 mg/day from week three. Her stay in hospital was complicated by a right distal tibioperoneal fracture which was surgically resolved.

She was admitted to the Intensive Care Unit due to respiratory failure, hypoxemia and a fever of 39 °C, with no response to pipercillin-tazobactam and ciprofloxacin initiated whilst there. Chest x-ray showed signs of heart failure without clear pneumonic infiltration. A transthoracic echocardiography was requested (TTE), with biventricular dysfunction being highlighted as the only pathology.

After 24 h stay in the ICU the patient's condition worsened which led to obligatory endotracheal intubation and a situation of cardiogenic shock. The TTE showed progressive impairment of the ejection fraction of left ventricle at 10%, together with generalised hypokinesia.

Surveillance of the different aetiologies leading to the development of cardiogenic shock was performed, including pulmonary thromboembolism, ischaemic cardiopathy, valvulopathies, sepsis-associated myocardial depression... they were all ruled out, with focus placed on myocarditis as the principal trigger factor.

Myocarditis is an acute inflammatory process the aetiology of which is linked to an infectious process (the most common viral cause) and/or an immune response (drugs, toxic agents). Clinical presentation is highly variable, from mild forms, even asymptomatic to more serious forms which involve heart failure, cardiogenic shock and death. Diagnosis is based on analytical tests (CK, troponine) and on imaging (electrocardiograms, TTE) although none is specific. During recent years magnetic resonance has become a non invasive technique of choice (84% sensitivity and 74% specificity), although the gold standard still continues to be heart biopsy.

The patient began with cardiogenic shock symptoms 3 weeks after initiating treatment with clozapine. Since other aetiological causes, such as viral and toxic were ruled out, the most plausible diagnostic impression was pharmacological.

Myocarditis from clozapine was described by Killian in 1999.[1] Genetic, environmental and/or clinical factors (new treatment, fast establishment of complete dose of medication or concomitant use with other drugs) may mean that the levels reached in the blood would be different. In approximately 80% of cases symptomatology appears during the first month of treatment.[2] Early suspicion and detention is vital for a fast management by associated morbimortality. The clinical characteristics were started between the second and third week of treatment and these include fever, dyspnoea, eosinophilia, increased LDH, CPK and troponin, together with non specific changes in the ECG, none of which were pathognomonic of the symptoms.

At present, benefits from the use of clozapine in patients with resistant schizophrenia are unquestionable but side effects must be known to optimise usage and to make it safe. Clozapine necessarily requires standardised haematological controls to avoid agranulocitosis, but there are other side effects such as myocarditis which could also have fatal

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