Letter to the editor

Archives of Psychiatry Research 2026;62:185-188

DOI:10.20471/sept.2026.62.02.10
Received February 2, 2025
Accepted after revision February 24, 2025

Caesarean Delivery as a Potential Predictor of Metabolic Changes in Psychosis Treatment

Sergej Nadalin[1,2], Mislav Škrobo[3], Ivan Ljoka[3], Ivan Majdandžić[4], Ante Silić[2,3]

[1]Department of Psychiatry, General Hospital "Dr. Josip Benčević", Slavonski Brod, Croatia, [2]School of Medicine, Catholic University of Croatia, Zagreb, Croatia, [3]Department of Psychiatry, University Hospital Center Sestre Milosrdnice, Zagreb, Croatia, [4]Department of Anesthesiology, Reanimatology and Intensive Care Medicine, General Hospital "Dr. Josip Benčević", Slavonski Brod, Croatia

Bacteria in the gut microbiota modulate the synthesis and functioning of gamma-aminobutyric acid, dopamine, and other neurotransmitters, and are also relevant in the regulation of insulin sensitivity [1,2]. The gut microbiota balance can be disrupted by both caesarean delivery and use of antipsychotic medication (particularly second generation antipsychotics, also known as atypical antipsychotics) [3,4]. Although evidence suggests that caesarean delivery is not associated with lifetime schizophrenia risk, some studies indicate that caesarean delivery might be associated with clinical features of this illness [5-8]. The FondaMental Academic Centers of Expertise for Schizophrenia conducted studies among chronic schizophrenia patients receiving antipsychotic medications in the French population, and investigated whether the type of delivery (caesarean or vaginal) might influence the age of schizophrenia onset, and symptom severity according to the Positive and Negative Syndrome Scale (PANSS), Calgary Depression Rating Scale for Schizophrenia, and Young Mania Rating Scale. They also investigated whether the delivery type might be associated with metabolic syndrome-related parameters—such as body mass index (BMI), waist circumference, plasma triglyceride and glucose levels, and nicotine dependence. Their results showed that patients delivered by caesarean section exhibited poorer premorbid intellectual functioning, as well as lower BMI and waist circumference, compared to those delivered vaginally. [6]. We have conducted studies among antipsychotic-medication-free patients from the Croatian population, to investigate whether the delivery type might influence PANSS psychopathology data, plasma lipid and glucose levels, body mass index, and nicotine dependence. We found that compared to patients born by vaginal delivery, those born by caesarean delivery exhibited significantly higher triglyceride levels and greater prevalence of nicotine dependence [7,8]. To date, no published study has addressed the potential association between delivery type and antipsychotic treatment. In the present study, we hypothesized that delivery type might be associated with antipsychotic-treatment-related changes in PANSS psychopathology, BMI, and plasma lipid and glucose levels.

We recruited 131 antipsychotic-naïve first-episode psychosis patients or nonadherent individuals with chronic psychosis. Schizophrenia was the most common diagnosis (112/131; 85.5 %). The patients' baseline characteristics are reported in our previous work [7,8]. The patients' diagnoses were verified by at least two psychiatrists, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), using a structured clinical interview. Antipsychotic-naïve patients had never previously received treatment with antipsychotic medication. Non-adherent chronic patients were noncompliant with their antipsychotic medication usage or had been off antipsychotic depot injections for at least

Correspondence to:
Sergej Nadalin M.D., Ph.D.
Department of Psychiatry, General Hospital "Dr. Josip Benčević"
Andrije Štampara 42, 35000 Slavonski Brod, Croatia
Phone. +385 35 201 835
E-mail: sergej.nadalin@medri.uniri.h

1 month, according to auto-anamnestic and hetero-anamnestic information. Written informed consent was obtained from all patients, and this study was approved by the Ethics Committees of the Medical Faculty of the University of Rijeka, Rijeka; the Clinical Hospital Center Rijeka, Rijeka; and the Clinical Hospital Center Sestre Milosrdnice, Zagreb.

For 8 weeks, patients received one or more of the following medications: clozapine (n = 53), risperidone (n = 32), aripiprazole (n = 30), paliperidone (n = 28), aripiprazole depot (n = 19), haloperidol (n = 18), fluphenazine (n = 11), and/or olanzapine (n = 7). Age of onset was defined as the patient's chronological age at their first hospital admission due to a psychotic episode, at which the diagnosis of psychosis was used. Baseline PANSS psychopathology was evaluated during a psychotic state of the illness requiring hospitalization. PANSS scales were divided into five symptom factors: positive (P1, P3, P6, and G9), negative (N2, N3, N4, N6, and G7), excitement (P4, P7, and G1), depression (G2, G3, and G6), and cognitive (G10 and G12) [9]. Plasma levels of total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, and glucose were measured using an Abbott Architect c8000 analyzer, at the Department of Clinical Chemistry in University Hospital Center Sestre Milosrdnice, Zagreb. BMI was calculated as weight in kilograms divided by height in meters squared. Statistical analyses were conducted using Statistica for Windows, version 14 (StatSoft, Inc., Tulsa, OK, USA), and p values of < 0.05 were considered significant. Mann-Whitney U tests were used to examine associations between delivery type and changes in mean PANSS psychopathology scores, plasma lipid and glucose levels, and BMI after antipsychotic treatment. We examined the association between changes in LDL cholesterol and delivery type by multiple regression analysis with adjustment for age, number of psychotic episodes, and BMI changes [10].

Among the 131 respondents, only 11 (8.4 %) were born by caesarean delivery. We found no association between delivery type and changes in PANSS psychopathology. However, delivery type was significantly associated with changes in LDL cholesterol levels. Specifically, compared to those born by vaginal delivery, patients born by caesarean delivery, manifested significantly higher increases in LDL cholesterol levels (0.8 ± 0.6 vs. 0.2 ± 0.5, $z = -2.32$, $p = 0.017$). Multiple regression analysis confirmed that LDL cholesterol increases were predicted by delivery type ($\beta = 0.28$, $F = 8.69$, $p = 0.004$), and revealed that the delivery type accounted for ~ 8.3 % of the variability in LDL cholesterol levels (multiple R2 change = 0.083).

The presently reported data indicate the intriguing possibility that an interaction between delivery type and antipsychotic medications might be useful for predicting metabolic-syndrome-related parameters upon antipsychotic treatment. Specifically, caesarean delivery might be a risk factor for increased LDL cholesterol levels upon antipsychotic treatment. Although the multiple regression analysis results suggested a relatively weak contribution of the delivery type to LDL cholesterol levels (multiple R2 change = 0.083), we observed a strong association between LDL cholesterol levels and delivery type (pmultiple regression = 0.004). Our previous study among unmedicated psychosis patients indicated that caesarean delivery might be a risk factor for increased triglyceride levels [7]. On the other hand, the study conducted among chronic schizophrenia patients on antipsychotic medications in the French population suggested that caesarean delivery might be a protective factor toward BMI and waist circumference [6]. These findings suggest a complex relationship between delivery type and schizophrenia, potentially influenced by metabolic pathways, treatment status, ethnic differences, and other factors. Further research with larger samples is needed to explore treatment responses to specific antipsychotic medications.

Acknowledgments

None.

Conflict of Interest

None to declare.

Funding Sources

None.

References

1. Mhanna A, Alshehabi Z. The microbiota-gut-brain axis and three common neurological disorders: a mini-review. Ann Med Surg (Lond). 2023;85:1780-3.
2. Semo D, Reinecke H, Godfrey R. Gut microbiome regulates inflammation and insulin resistance: a novel therapeutic target to improve insulin sensitivity. Signal Transduct Target Ther. 2024;9:35.
3. Zhang C, Li L, Jin B, Xu X, Zuo X, Li Y, et al. The effects of delivery mode on the gut microbiota and health: state of art. Front Microbiol. 2021;12:724449.
4. Kamath S, Hunter A, Collins K, Wignall A, Joyce P. The atypical antipsychotics lurasidone and olanzapine exert contrasting effects on the gut microbiome and metabolic function of rats. Br J Pharmacol. 2024;181:4531-45.
5. O'Neill SM, Curran EA, Dalman C, Kenny LC, Kearney PM, Clarke G, et al. Birth by caesarean section and the risk of adult psychosis: A population-based cohort study. Schizophr Bull. 2016;42:633-41.
6. Fond G, Bulzacka E, Boyer L, Llorca PM, Godin O, Brunel L, et al. Birth by cesarean section and schizophrenia: results from the multicenter FACE-SZ data-set. Eur Arch Psychiatry Clin Neurosci. 2017;267:587-94.
7. Nadalin S, Dević Pavlić S, Peitl V, Karlović D, Zatković L, Buretić-Tomljanović A. Vrsta poroda i komponente metaboličkog sindroma u bolesnika sa shizofrenijom koji ne primaju terapiju. Med Flum. 2021;57:437-43.
8. Nadalin S, Peitl V, Karlović D, Dević Pavlić S, Škrobo M, Uremović M, et al. Could the type of delivery contribute to clinical features of schizophrenia and nicotine dependence among patients who are not under antipsychotic treatment? Arch Psychiatry Res. 2022;58:91-8.
9. Wallwork RS, Fortgang R, Hashimoto R, Weinberger DR, Dickinson D. Searching for a consensus five-factor model of the Positive and Negative Syndrome Scale for schizophrenia. Schizophr Res. 2012;137:246-50.
10. Dayabandara M, Hanwella R, Ratnatunga S, Seneviratne S, Suraweera C, de Silva VA. Antipsychotic-associated weight gain: management strategies and impact on treatment adherence. Neuropsychiatr Dis Treat. 2017;13:2231-41.