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The impact of peri-natal stress on psychosis risk: results from the Bo-FEP incidence study

Tiziano De Matteis[1,2], Giuseppe D'Andrea[1,2], Jatin Lal[1,2], Domenico Berardi[2] and Ilaria Tarricone[1,3*]

Abstract

Objective: According to the gene-environment interaction model the pathogenesis of psychosis relies on an adverse neuro-socio-developmental pathway. Perinatal stress represents an important risk factor for the development of psychosis because of the increasingly evident interference with socio-neuro-development in the earlier phases of life. We aim to investigate the correlation of perinatal risk factors with the onset of psychosis with a case–control–incidence study.

Results: Patients (and their mothers) were eligible if they presented with first-episode psychosis at the Bologna West Community Mental Health Centre (Bo-West CMHC) between 2002 and 2012. The Bo-West CMHC serves a catchment area of about 200,000 people. The controls were recruited in the same catchment area and study period. 42 patients, 26 controls and their mothers were included. We collected the history of peri-natal stress and calculated crude and adjusted Odds Ratios for onset of first-episode psychosis. Adjusted logistic regression showed that psychosis onset was significantly associated with stressful situations during pregnancy, lower level of maternal physical health before or during pregnancy, use of anti-inflammatory drugs during pregnancy, and low level of maternal education. The results of our study suggest that stress during perinatal period increases the risk of developing psychosis.

Keywords: First-episode psychosis, Peri-natal stress, Obstetric complications, Risk of psychosis

Introduction

The pathogenesis of psychosis relies on several causal factors according to the gene-environment (GxE) interaction model [1–4]. Prenatal and perinatal complications represent important risk factors for the development of psychosis because they interfere with neurodevelopment [5].

Pre- and perinatal risk factors of psychosis in the offspring can be grouped as pregnancy-dependent or pregnancy-independent. Several of these variables, including the exposure to stressful or traumatic events during pregnancy [6–9], low socio-economic status (SES) [10, 11], and low level of maternal education [12], have been correlated with higher risk of psychotic onset in the offspring. Disadvantaged social conditions may be associated with a higher number of obstetric complications (OCs), more stressful life events, specific (tuberculosis and sexually transmitted diseases) and non-specific infections [13], potentially risky behaviors such as poor medical monitoring of pregnancy and alcohol and tobacco consumption, food deficiencies [14, 15].

Several studies have explored the effect of maternal diseases on psychosis onset in offspring, such as maternal influenza (especially in the first trimester of pregnancy) [16], infections from Rubella Virus, Toxoplasma gondii [17] and HSV type 2 [18]. Increased risk of psychosis in the offspring was also correlated with maternal inflammation markers, such as elevated levels of interleukin-8 and C-reactive protein [13, 19, 20]. Additionally, birth in late winter and early spring constitute a risk factor for psychosis [21–23].

*Correspondence: ilaria.tarricone@unibo.it
[3] Department of Medical and Surgical Sciences (DIMEC), University of Bologna; Clinica Medica, Policlinico Sant'Orsola-Malpighi, Via Masserenti 9, 40138 Bologna, Italy
Full list of author information is available at the end of the article

An increased risk of schizophrenia in offspring is associated with the mother's being very young or older than 34 years [24]. Likewise, the father's being older than 35 is associated with an increased risk of schizophrenia in offspring [25–27].

Epidemiological studies showed that OCs are associated with a double risk of schizophrenia in offspring [28, 29]. The main etiopathogenetic mechanism involved would seem to be hypoxia. [7, 10, 30].

Few studies have investigated simultaneously the effects of pregnancy-dependent vs pregnancy-independent risk factors on psychosis developing among offspring. The objective of our study is to analyze the prevalence and correlation with psychotic onset of pregnancy dependent and independent pre-, perinatal risk factors.

Main text

Methods

Recruitment

Patients between 18 and 64 years old with a first-episode psychosis (FEP) were identified among first accesses to the three CMHCs within tightly defined catchment areas in West–Bologna, Italy from January 2002 to December 2012 [31]. The inclusion criteria were based on those used in the World Health Organization (WHO) study [32]: i.e., presence of hallucinations, delusions, thought disorder, bizarre or disturbed behavior, negative symptoms, mania, or clinical suspicion of psychosis; absence of an organic cause or profound learning disability; and no previous contact with psychiatric services for psychotic symptoms. Case-notes were used to complete the Item Group Checklist (IGC), part of the Schedule for Clinical Assessment of Neuropsychiatry, Version 2.1 (SCAN; WHO, 1998), to collect symptom-related data at the time of presentation and 1 month later to ensure that cases met ICD-10 criteria for psychotic disorders [31].

Controls were healthy individuals and their mothers and were recruited from the same catchment area. To select a population-based sample of controls broadly representative of local populations in relation to age, gender, and ethnicity, a mixture of random and quota sampling was used. Individuals who agreed to take part were screened for a history of psychosis and were included only when they did not report past or current psychotic disorder [33].

Potential participants and their mothers were contacted after a preliminary opinion from the clinical psychiatrist in charge to evaluate whether they should be proposed for inclusion in the study. Interviews were also conducted on controls' mothers. The interview was conducted by a trained mental health operator.

Measures

Subjects' mothers were interviewed using the "Mother Interview", formulated within the Genetic and Psychosis project (GAP) [34]. This consists of three basic sections: Section A-Demographic Survey (collects socio-demographic information about family members of the subject, especially at the time of pregnancy and birth); Section B-Questionnaire on Obstetric Complications (Pathological and obstetrical history of the mother; Pregnancy Complications; Delivery Complications; Neonatal Complications); Section C-First stages of development (any problems in early childhood). In order to highlight the presence of OCs in the history of each case or control under examination, the Lewis-Murray Scale [30] was used on the data obtained from the interview with the mother.

The sociodemographic information on the subjects was collected through the Medical Research Council (MRC) socio-demographic schedule [35], which gathers sociodemographic data as well as information relating to substance use and migratory history. The subjects were also evaluated via the Cannabis Experience Questionnaire (CEQ) [33, 36] and the Family Interview for Genetic Studies (FIGS) [37].

Statistical analyses

The group comparison methods used include the Chi square test and Fischer's Exact test for categorical variables and one-way analysis of variance for continuous dependent variables. Logistic regression models were used to analyze associations between independent and dependent variables, as well as to estimate the odds ratio (OR)-when the data distribution made it possible- and confidence intervals at 95% (CI). Subsequently adjustments were made for confounding factors (age and sex) with multivariate logistic regression. All the statistical analyses were conducted with SPSS for Windows 23.0

Results

Forty-two patients, 26 controls, and their mothers were included (Table 1)

250 cases were initially recruited, but it was possible to interview the mothers in 42 cases (16.8%). In 208 cases no interview was possible because either the patients were no longer in contact with the service; their mothers were deceased, they were adopted, the mothers were abroad, clinicians did not recommend the interview, or patients and/or their mothers did not consent. The cases included were significantly younger than those not included (28.05 vs 32.65 $p = 0.006$) with no other difference between the two groups.

Table 1 Socio-demographics characteristics

	Cases	Controls
n (%)	42 (100)	26 (100)
Gender, n (%)		
Men **	26 (61.9)	9 (34.6)
Women **	16 (38.1)	17 (65.4)
Mean age of the participants (SD)	28.07 (8.52)	30.85 (5.98)
Origin, n (%)		
Natives	38 (90.5)	26 (100)
Emilia Romagna	28 (66.5)	11 (42.3)
Other regions	10 (23.8)	15 (57.7)
Migrants	4 (9.5)	0 (0.0)
Ethnicity, n (%)		
Caucasian	40 (95.2)	26 (100)
African	2 (4.8)	0 (0.0)
Social class (defined by the paternal working status at birth), generic, n (%)	39 (100)	25 (100)
Intermediate-high **	22 (56.4)	20 (80.0)
Low**	17 (43.6)	5 (20.0)
Social class (defined by the paternal working status at birth), specific, n (%)		
High-level managerial and professional activities	8 (20.5)	9 (36.0)
Low-level managerial and professional activity	2 (5.1)	2 (8.0)
Intermediate occupation	5 (12.8)	4 (16.0)
Employees/own small business	5 (12.8)	3 (12.0)
Low-level technical activities	2 (5.1)	2 (8.0)
Semi-routine occupations	4 (10.3)	0 (0.0)
Routine occupations	12 (30.8)	5 (20.0)
Unemployed	1 (2.6)	0 (0.0)
Family history of psychiatric diseases (1st degree relatives), n (%)	31 (100)	20 (100)
Yes	8 (25.8)	7 (35.0)
Family history of psychosis	1 (3.4)	0 (0.0)

*p < 0.1 e > 0.05; **p < 0.05 e > 0.001; ***p < o = 0.001

Sociodemographic characteristics of cases and controls were reported in Table 1. Cases were more frequently men (26, 61.9%) than controls (9, 34.6%, c sq = 4.79, p = 0.029), The mean age was 28.07 years (+ 8.52) at the time of onset. Greater prevalence of high and intermediate social class levels was found among controls (80% vs 56.4%, c sq = 3.75, p = 0.053). There were no other statistically significant differences among cases and controls.

Table 2 reports characteristics of mothers of cases and controls and frequency of the obstetric complications. The mean age of mothers at delivery was 26.88 years for cases and 28.46 years in controls. The mean paternal age was 31.08 for cases, and 31.81 for controls. Mothers were mostly married, working, homeowners, living with their partner and/or children. A more frequent history of medical disorders and use of drugs (12, 34.3% vs 3, 12.5%), particularly anti-inflammatory drugs (7, 20.6% vs 0, 0.0%), were more frequently found among mothers of cases compared with mothers of controls. Moreover, mother of cases (24, 57.1%) reported more frequently negative memories during pregnancy compared to mothers of controls (2, 7.7%). No other difference was found between mother of cases and mothers of controls.

The following associations were found to be significant by logistic regression analysis adjusted for sex and age:

- highly stressful situations during pregnancy (c sq = 16.62, p = 0.000), OR = 16.0 (95% CI 3.3–76.6; p = 0.001); the risk remains significant even when adjusted for age and gender in multivariate logistic regression analysis (OR = 23.8, 95% CI 4.2–134.2, p = 0.000);
- a lower level of maternal physical health before or during pregnancy (c sq = 16.62, p = 0.000), OR = 16 (95% CI 3.3–76.6; p = 0.001); the risk remains significant even when adjusted for age and gender in multivariate logistic regression analysis (OR = 16.8, 95% CI 3.3–86.0,p = 0.001).
- use of anti-inflammatory drugs during pregnancy (c sq = 5.61; p = 0.018).
- low level of maternal education (c sq = 5.49; p = 0.019), OR = 4.1(95% CI 1.2–14.2; p = 0.024); the risk remains significant even when adjusted for age and gender in multivariate logistic regression analysis (OR = 5.08, 95% CI 1.3–20.5, p = 0.023).

Experience of OCs prior to pregnancy was rare without significant differences between cases and controls

The use alcohol during pregnancy was no different between the groups and there wasn't any difference in cigarette consumption during pregnancy between cases and controls. Around half of the fathers smoked at home during pregnancy without any statistically difference. No mother admitted to having used any substance during pregnancy.

Most mothers nursed, in similar proportions between cases and controls. Patients' mothers breastfed for longer, for a mean of 6.85 months compared to 4.1 months for controls (t test = 2.083, p = 0.041). Alcohol was the most used substance (5, 14.3% of cases, 4, 17.4% of controls), followed by smoking (3, 8.1% in cases; 1, 4.3% in controls) and medication (3, 8.8% in cases; 2, 8.7% in controls). The

Table 2 Association between obstetric complications and first-episode psychosis

Health status of the mothers	Cases	Controls
n (%)	42 (100.0)	26 (100.0)
First child	29 (69.0)	15 (57.7)
Second child	8 (19.0)	8 (30.8)
Third or further child	5 (11.9)	3 (11.5)
Mean age of the parents at cases' births (SD)		
Mothers' age	26.88 (5.4)	28.46 (5.3)
Fathers' age	31.08 (6.06)	31.81 (5.7)
Mean age of the mothers at the interview (SD)	58.57 (9.5)	58.96 (5.4)
Maternal disorders history, n (%)	42 (100.0)	26 (100.0)
Negative***	20 (46.6)	24 (92.3)
Positive***	22 (52.4)	2 (7.7)
Endocrine-Metabolic disorders	5 (11.9)	0 (.0)
Cardio-vascular disorders	4 (9.5)	0 (0.0)
Respiratory disorders	2 (4.8)	0 (0.0)
Neurological disorders	1 (2.4)	0 (0.0)
Gynaecological disorders *	9 (21.4)	1 (3.8)
Other	9 (21.4)	2 (7.7)
Pathological obstetric history, n (%)	42 (100.0)	26 (100.0)
Not applicable	29 (69.0)	14 (53.8)
Negative	10 (23.8)	10 (38.5)
Positive	3 (7.1)	2 (7.7)
OCs, n (%)	42 (100.0)	26 (100.0)
Present	27 (65.9)	20 (76.9)
Absent	14(34.1)	6 (23.1)
Negatives memories (e.g. trauma), n (%)	42 (100.0)	26 (100.0)
No***	18 (42.9)	24 (92.3)
Yes***	24 (57.1)	2 (7.7)
Use of drugs-alcohol-substances in pregnancy		
Not-users	24 (57.1)	14 (53.8)
Users	18 (42.9)	12 (46.2)
Alcohol during pregnancy, n (%)	15 (35.7)	11 (42.2)
Monthly or less	3 (7.1)	1 (3.8)
2–3 time/month	5 (11.9)	1 (3.8)
2–3 times/week	5 (11.9	8 (30.8)
Every day	2 (4.8)	1 (3.8)
Smoking during pregnancy, n (%)	7 (15.8)	3 (11.5)
6–9 sigarettes/die	6 (14.3)	2 (7.7)
10–20 sigarettes/die	1 (2.4)	1 (3.8)
Other smokers at home	18 (43.9)	14 (56.0)
Other Substances during pregnancy, n (%)	0 (0.0)	0 (0.0)
Medicinal drugs during pregnancy, n (%)	35 (100.0)	24 (100.0)
Yes*	12 (34.3)	3 (12.5)
No*	23 (65.7)	21 (87.5)
Anti-inflammatory drugs**	7 (20.6)	0 (0.0)

*p < 0.1 e > 0.05; **p < 0.05 e > 0.001; ***p < o = 0.001

use of potentially risky substances (alcohol, medications and drugs) was not significantly different between cases and controls.

Infections during pregnancy were reported by 3 mothers (11.5%) of controls and 2 (4.9%) of patients. For both cases and controls, urogenital infection and influenza were the most common.

An excessive weight gain was found in 6 (14.6%) mothers of patients and 3 (11.5%) of controls.

There was a slightly higher incidence of OCs in mothers of patients than in those of controls without any statistically significant difference (14, 34.1%, vs 6, 23.1%; c sq = 0.931, p = 0.335). Eight out of 14 OCs (19%) among cases and 4 (15%) out of 6 among controls occurred during pregnancy and consisted of a threat of abortion or ante-partum hemorrhage. OCs during delivery and postnatal period numbered 11 in cases and 7 in controls.

Discussion

Our study showed that pre-natal—independent of pregnancy—risk factors, related to stress-trauma and poor maternal health conditions during pregnancy are associated with psychosis onset in offspring. In addition, we found a lower level of education in mothers of offspring with FEP.

One possible mediator between adverse environmental conditions during pregnancy and psychosis development in offspring may be the high level of stress experienced in pregnancy, as reported by mothers of our patients, with an age and gender adjusted OR of 24. Examples of stress factors reported by mothers in the Mother Interview in our study are relational problems in family life, major health problems, need to work hard or in unhealthy environments. Stress during pregnancy correlates with changes in the hypothalamus-pituitary axis that regulates cortisol secretion in the offspring. Maternal glucocorticoids seem to have a great effect on the child's stress with dysregulation in the dopaminergic system and a depression of its axis would lead to negative symptoms and cognitive symptoms [38]. In addition, there may be direct action on the expression of NMDA receptors, which are reduced in the hippocampus of patients undergoing prenatal stress and could predispose to greater stress vulnerability in later periods of perinatal development [4, 39].

Our finding of a greater use of anti-inflammatory drugs by mothers of patients during pregnancy, especially acetylsalicylic acid, is consistent with the evidence that their use during pregnancy correlates with neuro-development disorders. Its action leads to a deficiency of prostaglandin and essential fatty acids (constituents of Phospholipid membranes) which could alter the membrane structure in fetal brain development [40].

We would have expected a significant difference between cases and controls in the frequency of possible pregnancy-related risk factors such as OCs evaluated by the Lewis Murray Scale. As evidenced by previous studies, such events are approximately twice as frequent in those suffering from psychosis than in the general population [28]. It should be noted that OCs are rare events, which need to be better studied in larger samples. According to the Italian Certificate of Birth Assistance data of 2009, only 0.8% of newborns, within 5 min of birth, report an Apgar index of < 7 indicative of severe depression and therefore neonatal suffering and high mortality risk, which corresponds to approximately 1% of babies born weighing < 1500 g.

Conclusions

Despite the limitations, this study offers interesting results, especially regarding the role of pre-natal independent-of-pregnancy risk factors in the development of psychosis. Of interest are the correlations between psychosis and:

1. Poor health during pregnancy, including the use of analgesics and anti-inflammatory drugs in pregnancy and impaired physical health of the mother at the time of conception;
2. Exposure to stressful or traumatic events.

The results of our study suggest that from the pre-natal phase onward attention should be given on avoiding stress and preventing its adverse effects on mother and child health, i.e. acting early in the gene-environment interaction. The role of genetic vulnerability will be better illustrated when the results of the EUGEI study are published/discussed. We therefore believe that potential risk factors before and during pregnancy, and not just OCs, should be studied and a preventive/early intervention strategy should be implemented. A more in-depth study of these risk factors and a more multidisciplinary approach to pregnancy-care could lead to primary prevention interventions targeting psychosis, such as raising the awareness of mothers and their social and familiar context about the harmful effect of exposure to stress.

Limitations

- The number of participants is relatively small;
- The two groups differed in gender distribution, with men being more represented in the case group and women in the control group;
- The nature of the interviews and retrospective investigation made the study vulnerable to recall bias.

Abbreviations

SES: Socio-economic status; OCs: Obstetric complications; HSV: Herpes simplex virus; FEP: First-episode psychosis; CMHC: Community mental health centre; ICD: International classification of diseases; WHO: World Health Organization; GAP: Genetic and psychosis project; MRC: Medical Research Council; CEQ: Cannabis Experience Questionnaire; FIGS: Family Interview for Genetic Studies; OR: Odds ratio; CI: Confidence interval; c sq: Chi square.

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Authors' contributions

IT and DB designed the study. IT obtained funding. TD, JL and GD obtained the data. IT and DB coordinated the data management. TD and GD prepared the data and did the statistical analyses. TD, GD, and IT interpreted the statistical analyses. TD and GD wrote the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The data supporting the findings of this study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Ethical approval was obtained from the local Research Ethics Committee ("Comitato Etico dell'Azienda Ospedaliera Universitaria di Bologna" of the Sant'Orsola-Malpighi Policlinic) with reference number 113/2006/U in accordance with the Declaration of Helsinki. All participants provided written informed consent before participating in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author details

[1] Bologna Transcultural Psychosomatic Team (BoTPT), Department of Medical and Surgical Sciences, Alma Mater Studiorum Bologna University, Bologna, Italy. [2] Department of Biomedical and Neuromotor Sciences, Alma Mater Studiorum, Bologna University, Via Giovanni Masserenti, 9 – Pavillon 11, 40138 Bologna, Italy. [3] Department of Medical and Surgical Sciences (DIMEC), University of Bologna; Clinica Medica, Policlinico Sant'Orsola-Malpighi, Via Masserenti 9, 40138 Bologna, Italy.

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