A Sex-Specified Effect of Obstetrical Complications in Symptoms of Schizophrenia

Bernard J. Gallagher III [1], Brian J. Jones [1], Kristen E. Eaton [1]

Abstract

Research on obstetrical complications (OCs) reports a connection with the development of more severe (negative) schizophrenic symptoms. To date, no study has tested to see if this association varies by sex. A large sample (n=786) of patients from a state hospital population in the United States was screened for study variables. Statistical tests employed were crosstabular analysis and analysis of variance. The central finding is a significant connection between OCs and negative symptoms for females but not for males. The authors speculate that there may be differences in the ways by which male and female fetuses respond to OCs or a distinction between the sexes in genetic predisposition toward severe schizophrenia.

Key Words: Schizophrenia, Gender Differences, Obstetrical Complications, Positive Symptoms, Negative Symptoms

Introduction

Obstetrical Complications and Schizophrenia

Obstetrical complications (OCs) are a regularly reported correlate of schizophrenia (1-3). Numerous studies with different types of designs and samples report that deviations from the normal course of pregnancy are associated with adult schizophrenia in offspring (4-7). The first hint of a connection between birth complications and schizophrenia occurred in the early twentieth century. Since then, research on OCs and schizophrenia has focused on the role of low birth weight, studies of high-risk groups, brain imaging studies, case-control studies, and population-based studies (8).

Since OCs can potentially damage the brain during pregnancy or delivery (9, 10), they may be more common in schizophrenic patients with early age of onset. This hypothesis is based on the expectation that brain injuries are not likely to remain latent for extended periods of time. Indeed, a meta-analysis based on the data of eleven research groups indicates that schizophrenic patients with early onset are much more likely than their later-onset counterparts to have had their gestation or birth complicated by an OC (11).

Regardless of age of onset or severity of symptoms, patients with schizophrenia are clearly more likely to show a history of OCs than control subjects. In fact, Preti et al. (12) report that schizophrenic patients are five times more likely to have suffered an antecedent OC of a severe nature than are normal "healthy" people with very similar birth characteristics. And three population-based studies conducted within a Sweden-wide cohort of all children born during 1973–79 report that adverse perinatal events are more strongly associated with schizophrenia than with any other form of psychosis (13). The few studies that failed to substantiate a relationship between OCs and the later development of schizophrenia used unique methodologies, which are difficult to compare with results from other studies (3).

The types of OCs investigated by different studies are wide and varied. Byrne et al. (14) show that increased risk for schizophrenia is associated with prematurity, manual

[1] *Department of Sociology, Villanova University, Villanova, PA, USA*

Address for correspondence: Kristen E. Eaton, Villanova University, 800 Lancaster Avenue, SAC 204, Villanova, PA 19085, USA
Phone: 610-519-4785; Fax: 610-519-6319;
E-mail: bernard.gallagher@villanova.edu

Submitted: February 2, 2012; Revised: March 11, 2012; Accepted: June 15, 2012

Clinical Implications

It has been established that obstetrical complications (OCs) are associated with brain damage. This, in turn, has a role in the pathogenesis of some cases of schizophrenia (9). There is also literature linking brain abnormality with negative symptoms, a presentation of schizophrenia with poor prognosis (18, 19). The central finding of the present study further pinpoints the connection between OCs and negative symptomatology. Specifically, we find that the connection is present for females and not for males. What is the underlying basis for this gender-specific phenomenon? We offer two hypothetical explanations: first, our finding may connect with studies reporting that the male fetus is more fragile than the female fetus. Consequently, an OC may be more likely to prevent birth among males in the first place, whereas a similar insult to a female fetus may not result in spontaneous abortion but rather life with a brain abnormality. Simply stated, the males are more likely to die and the females are more likely to end up being psychotic.

The second hypothetical explanation for our gender-specific finding of the connection between OCs and negative symptomatology is not inconsistent with the fact that the male fetus is more fragile. In fact, it is an independent interpretation. We hypothesize that there may be separate etiologies of negative symptoms for male and female schizophrenics. One causal route may be genetic and the other may be obstetrical. As suggested in this study, the causal route for females is an insult to the fetal brain inflicted by OCs. Other researchers suggest that negative symptoms in men stem from a greater biological vulnerability caused by stronger genetic penetrance (54). Clearly, there is much more research needed to untangle the complex interplay of gender, genetics, and OCs in the genesis of schizophrenia with negative symptoms.

extraction, length of birth and birth weight below 1,999 grams. Dalman et al. (15) find a similar risk connected with malnutrition during fetal life, extreme prematurity, and hypoxia. Clarke et al. (16), summarizing the literature on OCs and increased risk for schizophrenia, report the most common *groups* of OCs. They include fetal growth retardation (lower birth weight and smaller head circumference), fetal perinatal hypoxia (a cluster of OCs involving oxygen deprivation), and prenatal complications (prenatal stress, intrauterine malnutrition, and prenatal infection). And a meta-analysis of twelve studies (17) uncovers significant associations between schizophrenia and premature rupture of membranes, gestational age shorter than thirty-seven weeks and the use of resuscitation or incubator. The most likely common denominator in these various OCs is hypothesized to be hypoxia brain damage (3, 17).

Some argue that because, in the general population, the vast majority of people with OCs do not develop schizophrenia, OCs are neither necessary nor sufficient causal factors for schizophrenia and should instead be described as component causes (16). Regardless of the nature and degree of their causal links with schizophrenia, OCs clearly provide an additional factor that should be taken into consideration when identifying risk factors for this psychosis (4).

Obstetrical Complications and Negative Symptoms

If OCs have the potential to cause brain damage, is it possible that OCs connect with negative symptomatology? Indeed, schizophrenia with negative symptoms—a condition connected with poor prognosis and diminished responsiveness to medications compared to schizophrenia with positive symptoms—has been linked with an abnormality in the actual structure of the brain (18, 19). This is a compelling reason why negative symptomatology is included as a major variable in this study. Here we refer to type of schizophrenia in two ways, according to types of symptoms: negative form and positive form. To date, there has been a paucity of studies examining *type* of schizophrenia and OCs (20). Our recent research has been an exception in that regard. We analyzed data from a large sample (n=437) of patients from a state hospital population in the U.S. and found a significant association between OCs and negative symptoms, but only for patients from a lower social class of origin (21).

Gender and Symptoms of Schizophrenia

Numerous studies have tested for gender differences in symptoms of schizophrenia. A majority of those studies report that male schizophrenics are more likely to manifest negative symptoms than their female counterparts who have higher rates of positive symptoms (22-24). Leung et al. (25), in a review of the literature on gender differences in schizophrenia, reached the conclusion that males show more negative symptoms (such as social withdrawal, blunted affect, poverty of speech, and amotivation) with greater structural brain and neurophysiological abnormalities. Related assessments of gender differences in symptomatology also report greater *severity* of negative symptoms among males (26) as well as poor outcome (27, 28).

While a majority of studies report a greater propensity for negative symptoms among male schizophrenics, there are also contradictory findings of no significant differences in symptomatology between male and female patients (29,

30). This is an interesting fact because it leads to the question of possible intervening variables that may produce the sex difference in symptoms. Indeed, our earlier research uncovered a reduced risk for negative symptoms among males born into nonpoor families (21). In that study, social class of origin and gender were co-associated with type of schizophrenia. Clearly, gender differences in schizophrenic symptoms are based on factors that are not fully understood. In fact, research to date begs for investigations of previously unexamined interconnections. This study is a response to that call.

The major hypothesis of the present study is that there is a significant association between OCs, schizophrenic symptoms, and gender. This study is unusual because it simultaneously examines the interaction of OCs and symptoms with gender. Other researchers have looked at the relationship between symptoms of schizophrenia and gender (20, 21), but this is the first study to test for an association between those two variables *and* OCs.

Methods

Data for this study have been taken from the cumulative anonymous medical records of 786 schizophrenic patients discharged from Norristown State Hospital (NSH) in Pennsylvania (United States) between 1984 and 1990. Diagnostic procedures employed multidisciplinary evaluations with periodic review. Specific criteria for index diagnosis are based on the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM)* (31).

Upon admission, patients were evaluated by staff psychiatrists and other members of a multidisciplinary team within forty-eight hours for diagnosis and treatment plan purposes. Later, diagnostic reviews were conducted for each patient every three months, or as needed, during hospitalization. Since some patients have been discharged and readmitted over time, we employed a combination of three operational measures to enhance longitudinal analysis of symptom stability. The measures included clinical assessments by NSH staff at intake and during last hospital stay, as well as *DSM* diagnosis at last discharge.

Clinical Assessments

In addition to diagnosis by *DSM* standards, NSH staff professionals further categorized patients into negative (e.g., symptoms such as mutism) and positive (e.g., symptoms such as hallucinations) subtypes. Subtyping is based on diagnosticians' judgments of clear presentation of positive or negative features at intake and during last hospital stay. Classification into these subtypes is based on positive and/or negative features of many individuals with schizophrenia (32). It is also compatible with research centering on "deficit/nondeficit schizophrenia." Deficit schizophrenia is an older terminology used to describe long-term patients with a persistent negative presentation. The division of schizophrenia into either "deficit/nondeficit" or "negative/positive" subtypes has yielded many important substantive findings about schizophrenia (33-35). Subtyping in this study is enhanced by chart materials with detailed patient symptomatology.

In addition to subtyping drawn from patient files, a number of positive and negative scales have been retrospectively applied from chart materials. They include the Scale for the Assessment of Negative Symptoms (SANS) (36), the Scale for the Assessment of Positive Symptoms (SAPS) (36), and the Positive and Negative Syndrome Scale (PANSS) (37). Although some may question the validity and reliability of chart-based assessments of negative and positive symptoms, we do not think these are serious problems in this study. It was standard procedure at NSH to require that interviewer observation of the patient be completely and directly recorded onto the charts. Therefore, the clinical assessments were solely conducted by NSH staff professionals, and we retrospectively applied the identical assessments to our sample. Both the original assessments at NSH and our replication of those assessments were conducted independently of patient history of OCs. The literature reports that the retrospective application of the SANS, SAPS and PANSS can be completed from chart materials if the latter are sufficiently detailed (38, 39). Such was the case in the present study.

One of the issues we faced was how to deal with diagnoses that changed over time. This proved to be a minor problem, since this type of discrepancy rarely occurred and, when it did occur, we simply eliminated the case from the sample. Thus, diagnosis is operationalized from three temporal sources: clinical assessment at first intake, during last hospital stay, and *DSM* diagnosis at last discharge. The temporal points of these measurements not only permit the observation of symptom stability over time, but also reflect studies cited earlier that schizophrenia patients who show *persistent* negative symptoms are an important subgroup with low-remission rates (40-44).

Negative/positive assessments were conducted by three independent raters. Two of the raters are experts in the field; one is a clinical psychologist and the other is a psychiatric sociologist. Consensus was reached on the classification of all included cases. Thus, interrater reliability is one hundred percent because, in the rare instances where there was disagreement, the cases were dropped. We also eliminated cases in which extrapyramidal complications were present.

As noted above, patients who did not clearly present as negative or positive were not included in this study. Individuals who had both positive and negative symptoms were

excluded. Thus, a patient was cross verified as negative only if chart materials reflected presentation of negative symptoms at first admission and during the last hospital stay and the index diagnosis was *DSM* "chronic" at discharge.

Obstetrical Complications

Like socioeconomic status (SES), data about OCs were obtained from the "social history" section of the hospital records. Nine obstetrical complications appeared in these accounts: maternal health problems during pregnancy, prenatal alcohol abuse, prenatal drug abuse, prenatal violence, premature birth, unusually long labor, breech birth, forceps delivery, and other delivery complications. Each OC was rare, almost always in single digit percentages; this rendered statistical tests of any particular complication untenable.

Prevalence of obstetrical complications was probably underestimated in the social histories due to recall problems since, by the time of admission, several decades would have elapsed since the patients were born. Obstetrical histories were provided by first-degree relatives, which usually, but not always, included the patient's mother. There was an interview format which included questions about OCs. Studies of the effect of maternal recall bias of OCs in research on schizophrenia have produced mixed results. One study suggested that schizophrenic patients had higher rates of OCs recalled by their mothers than controls (45). Another study found no evidence of positive recall bias as mothers of offspring with schizophrenia reported fewer complications than indicated on their obstetric records (46). Additionally, there is no reason to believe that recall bias in the present study will differentially affect the other variables (sex and symptomatology) in the research model to produce misleading effects.

Data Analysis

Type of schizophrenia, the dependent variable in the present model, is coded as a simple dichotomy such that 0=positive and 1=negative schizophrenia. The other variables in the model are sex of patient and, of course, obstetrical complications as the independent variable. Each of the nine complications identified above were relatively rarely reported events, so straightforward indexing—i.e., just adding up the number of OCs per patient—turned out to be fruitless because multiple OCs were too rare to permit meaningful statistical testing.

Therefore, two different breakdowns of OCs are utilized in the successive stages of analysis. The first separates patients with *at least one* OC in their social histories from those with none. This is the version of the independent variable for crosstabular analyses. Stage two of the analysis will employ analysis of variance (ANOVA) to facilitate direct testing of statistical interaction not available in crosstabulation. For the ANOVA test, the OC breakdown will be none, one and two or more reported OCs rather than a complete indexing for the reason offered above. Calculations are performed using the MicroCase data analysis system.

Results

Crosstabular Analysis

Table 1 displays the crosstabulation of obstetrical complications by schizophrenic subtype for males in the sample. Observe that in the top row—labeled "No," meaning no OCs—the prevalence of negative symptoms is 29.3%. In the "Yes" row—indicating that at least one OC is in the patient's background—the comparable percentage is 28.7%. Given the nearly identical percentages of the top and bottom rows, there is no surprise that the chi-square test yields no evidence of effect (x^2=0.017, p=.897). For sample males, OC history is unrelated to type of schizophrenia.

Table 1 Type of Schizophrenia by Obstetrical Complications for Males

Obstetrical Complications	Type of Schizophrenia (n=579)	
	Positive	Negative
No	328 (70.7%)	136 (29.3%)
Yes	82 (71.3%)	33 (28.7%)

X^2=0.017, p=.897

Table 2 for sample females exhibits a radical shift in the data pattern. The "No" row again shows a prevalence percentage in the mid-twenties, but that figure nearly doubles in the "Yes" row. 46.2% of women who had one or more OCs have a negative diagnosis. The direct chi-square test of this difference is indeed statistically significant (x^2=7.347, p=.007), and strongly suggests an elevated risk for females *only*.

Table 2 Type of Schizophrenia by Obstetrical Complications for Females

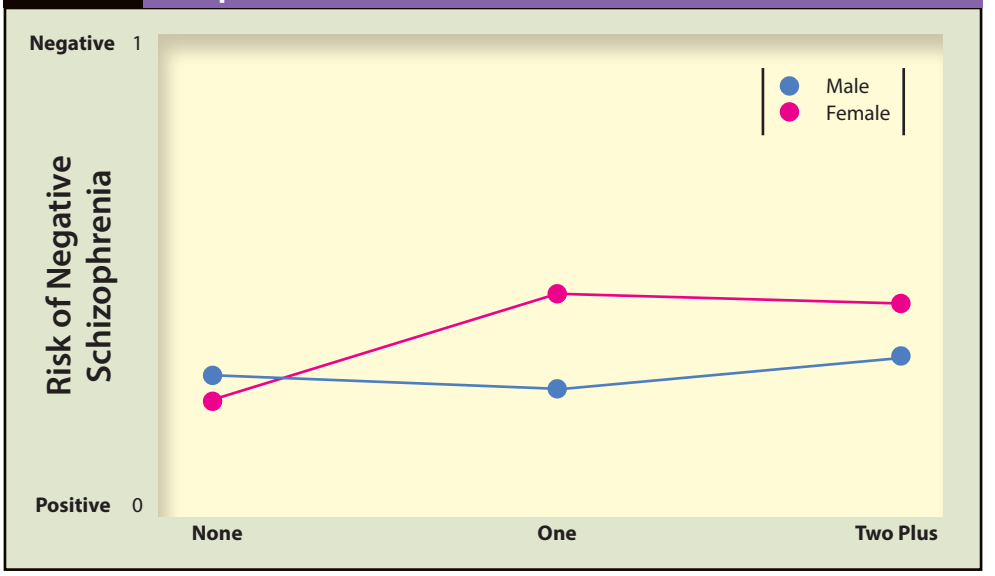
Obstetrical Complications	Type of Schizophrenia (n=207)	
	Positive	Negative
No	127 (75.6%)	41 (24.4%)
Yes	21 (53.8%)	18 (46.2%)

X^2=7.347, p=.007

Analysis of Variance

A somewhat more sophisticated appraisal of the hypothesis is permitted by the analysis of variance test displayed in Figure 1. The Y-axis represents the risk of negative (top) vs. positive (bottom) subtype calculated as a simple probability. The height of a given dot represents the mean risk for a

Figure 1 ANOVA of Risk of Negative Schizophrenia by Obstetrical Complication for Males and Females



given category of patient; the higher the dot, the higher the risk of negative diagnosis. On the X-axis are three categories for the independent variable: "None" indicates no history of OCs, "One" indicates a single complication, and "Two Plus" indicates more than one OC. With a dichotomous dependent variable (0=positive, 1=negative) and, in effect, categorical independent variables, this is an appropriate subject for ANOVA.

Note that the male line is virtually flat, which means that the dots representing risk of negative subtype change little from category to category of the independent variable. Not so for the female line. The lowest risk by far is above the "None" category, then it rises significantly to the right. The risk of negative subtype soars above the "One" OC category, then changes little in the highest "Two Plus" category. The substantive interpretation is that *any* OC exposure elevated female risk of negative diagnosis, but *multiple* exposures makes no further difference; and, visually, there is no such effect for male patients. To bolster the visual with the statistical, the ANOVA test of the "Sex-OC effect" is statistically significant (F=3.025, p=.049). As suggested by the crosstabular analysis and as directly tested here, there is a sex-specified effect such that *OCs elevate the risk of negative schizophrenia for females, but not for males.*

Two refinements of this central conclusion are in order. First, it should be noted that the interaction effect just tested is even stronger if the independent variable is reduced to a simple dichotomy as in the crosstabulations (F=5.746, p=.017). The reason for expanding the independent variable is to determine whether multiple OCs do indeed magnify risk for either sex, and the answer is clearly no. Breaking out the third category, however, attenuated cases (only 9 females had "Two Plus" OCs), thus weakening the effect.

A second related refinement concerns specific OCs. Given the emerging finding that a single OC makes the sex-specific difference, each of the nine complications was separately inspected to perhaps find a lone culprit. None was found. The numbers, particularly when broken down by sex, were very small and failed to resolve into a single explanation. It would appear that any one OC exacerbates female risk.

Discussion

It has been established that OCs are associated with brain damage. This, in turn, has a role in the pathogenesis of some cases of schizophrenia (9). There is also literature linking brain abnormality with negative symptoms, a presentation of schizophrenia with poor prognosis (18, 19). The central finding of the present study further pinpoints the connection between OCs and negative symptomatology. Specifically, we find that the connection is present for females and not for males. What is the underlying basis for this gender-specific phenomenon? We offer two hypothetical explanations: first, our finding may connect with studies reporting that the male fetus is more fragile than the female fetus. Consequently, an OC may be more likely to prevent birth among males in the first place, whereas a similar insult to a female fetus may not result in spontaneous abortion but rather life with a brain abnormality. Simply stated, the males are more likely to die and the females are more likely to end up being psychotic.

There is a lot of evidence to support the "relative fragility" explanation. Male fetuses are more likely to result in a premature rupture of the embryonic sac and suffer from un-

timely and difficult deliveries (47). Pregnancies of male fetuses are also associated with higher rates of labor dystocia, cord problems, fetal distress and significantly higher rates of nonreassuring fetal heart rate problems, all of which increase the likelihood of perinatal mortality (48). The list of elevated risk factors connected with male fetuses is lengthy and beyond the scope of this article. However, virtually all studies of the relative fragility of the male fetus report that male sex is an independent risk factor for adverse pregnancy outcome (49-52). Most germane to the present study is the established fact that the male fetus is at greater risk of death from almost all OCs that can occur before or during birth (53).

The second hypothetical explanation for our gender-specific finding of the connection between OCs and negative symptomatology is not inconsistent with the fact that the male fetus is more fragile. In fact, it is an independent interpretation. We hypothesize that there may be separate etiologies of negative symptoms for male and female schizophrenics. One causal route may be genetic and the other may be obstetrical. As suggested in this study, the causal route for females is an insult to the fetal brain inflicted by OCs. Other researchers suggest that negative symptoms in men stem from a greater biological vulnerability caused by stronger genetic penetrance (54).

Clearly, there is much more research needed to untangle the complex interplay of gender, genetics, and OCs in the genesis of schizophrenia with negative symptoms. As mentioned earlier, social class of origin may play an etiological role. Our *recent* research established a connection between OCs, negative symptoms and lower social class of origin (21). Additionally, our earlier research uncovered a curiously reduced risk for negative symptoms among males born into nonpoor families (55). We could not use SES as a covariate in this study because cell sizes became too small. The real explanations for the relationships above demand more studies that not only attempt to replicate those findings but also take them further into the depths of the procreational process from conception to birth (56).

The present study has two unique strengths. First, it includes a large number of different types of OCs. They were carefully provided by first-degree relatives, which almost always included the patient's mother. Second, the specification of schizophrenic symptoms is determined through multiple forms of assessment that examine changing symptomatology over time. However, the data set employed in this study has limitations. It only includes patients from a single state mental hospital in the northeastern United States. Additionally, it does not include information about maternal infection during early trimesters, a potentially relevant variable. Consequently, the study findings must be considered as exploratory rather than definitive.

References

1. Brixey SN, Gallagher BJ 3rd, McFalls JA Jr, Parmalee LF. Gestational and neonatal factors in the etiology of schizophrenia. J Clin Psychol 1993;49(3):447-456.
2. Geddes JR, Lawrie SM. Obstetric complications and schizophrenia: a meta-analysis. Br J Psychiatry 1995;167(6):786-793.
3. McNeil TF, Cantor-Graae E, Ismail B. Obstetric complications and congenital malformation in schizophrenia. Brain Res Brain Res Rev 2000;31(2-3):166-178.
4. Ballon JS, Dean KA, Cadenhead KS. Obstetrical complications in people at risk for developing schizophrenia. Schizophr Res 2008;98(1-3):307-311.
5. Rosso IM, Cannon TD. Obstetric complications and neurodevelopmental mechanisms in schizophrenia. In: Cicchetti D, Walker EF, editors. Neurodevelopmental mechanisms in psychopathology. London: Cambridge University Press; 2003. p. 111-137.
6. Cannon TD. On the nature and mechanisms of obstetric influences in schizophrenia: a review and synthesis of epidemiologic studies. Internat Rev Psychiatry 1997;9:387-398.
7. McNeil TF. Obstetric factors and perinatal injuries. In: Tsuang MT, Simpson JC, editors. Handbook of schizophrenia: nosology, epidemiology and genetics. Amsterdam: Elsevier; 1988. p. 75-89.
8. Cannon M, Jones PB, Murray RM. Obstetrical complications and schizophrenia: historical and meta-analytic review. Am J Psychiatry 2002;159(7):1080-1092.
9. Kunugi H, Nanko S, Murray RM. Obstetric complications and schizophrenia: prenatal underdevelopment and subsequent neurodevelopmental impairment. Br J Psychiatry Suppl 2001;40:s25-29.
10. Zornberg GL, Buka SL, Tsuang MT. The problem of obstetrical complications and schizophrenia. Schizophr Bull 2000;26(2):249-256.
11. Verdoux H, Geddes JR, Takei N, Lawrie SM, Bovet P, Eagles JM, et al. Obstetric complications and age at onset of schizophrenia: an international collaborative meta-analysis of individual patient data. Am J Psychiatry 1997;154(9):1220-1227.
12. Preti A, Cardascia L, Zen T, Marchetti M, Favaretto G, Miotto P. Risk for obstetric complications and schizophrenia. Psychiatry Res 2000;96(2):127-139.
13. Hultman CM, Sparen P, Takei N, Murray RM, Cnattingius S. Prenatal and perinatal risk factors for schizophrenia, affective psychosis, and reactive psychosis of early onset: case-control study. BMJ 1999;318(7181):421-426.
14. Byrne M, Agerbo E, Bennedsen B, Eaton WW, Mortensen PB. Obstetric complications and risk of first admission with schizophrenia: a Danish national register based study. Schizophr Res 2007;97(1-3):51-59.
15. Dalman C, Allebeck P, Cullberg J, Grunewald C, Koster M. Obstetric complications and the risk of schizophrenia: a longitudinal study of a national birth cohort. Arch Gen Psychiatry 1999;56(3):234-240.
16. Clarke MC, Harley M, Cannon M. The role of obstetric events in schizophrenia. Schizophr Bull 2006;32(1):3-8.
17. Geddes JR, Verdoux H, Takei N, Lawrie SM, Bovet P, Eagles JM, et al. Schizophrenia and complications of pregnancy and labor: an individual patient data meta-analysis. Schizophr Bull 1999;25(3):413-423.
18. Nasrallah HA, Weinberger DR. Neurology of schizophrenia. In: Nasrallah HA, Weinberger DR, editors. Handbook of schizophrenia: I. Amsterdam: Elsevier; 1990.
19. Andreasen NC, Arndt S, Alliger R, Miller D, Flaum M. Symptoms of schizophrenia: methods, meanings, and mechanisms. Arch Gen Psychiatry 1995;52(5):341-351.
20. Kotlicka-Antczak M, Gmitrowicz A, Sobow TM, Rabe-Jablonska J. Obstetric complications and Apgar score in early-onset schizophrenic patients with prominent positive and prominent negative symptoms. J Psychiatric Res 2001;35(4):249-257.
21. Jones BJ, Gallagher BJ, Moss DM, McFalls JA. Obstetrical complications, social class and type of schizophrenia. Clin Schizophr Relat Psychoses 2011;5(1):33-39.
22. Castle DJ, Murphy RM. The neurodevelopmental basis of sex differences in schizophrenia. Psychol Med 1991;21(3):565-575.

23. Maric N, Krabbendam L, Vollebergh W, de Graaf R, van Os J. Sex differences in symptoms of psychosis in a non-selected, general population sample. Schizophr Res 2003;63(1-2):89-95.
24. Willhite RK, Niendam TA, Bearden CE, Zinberg J, O'Brien MP, Cannon TD. Gender differences in symptoms, functioning and social support in patients at ultra-high risk for developing a psychotic disorder. Schizophr Res 2008;104(1-3):237-245.
25. Leung A, Chue P. Sex differences in schizophrenia: a review of the literature. Acta Psychiatr Scand Suppl 2000;401:3-38.
26. Schultz SK, Miller DD, Oliver SE, Arndt S, Flaum M, Andreasen NC. The life course of schizophrenia: age and symptom dimensions. Schizophr Res 1997;23(1):15-23.
27. Roy MA, Maziade M, Labbe A, Merette C. Male gender is associated with deficit schizophrenia: a meta-analysis. Schizophr Res 2001;47(2-3):141-147.
28. Bottlender R, Jager M, Groll C, Strauss A, Moller HJ. Deficit states in schizophrenia and their association with the length of illness and gender. Eur Arch Psychiatry Clin Neurosci 2001;251(6):272-278.
29. Usall J, Araya S, Ochoa S, Busquets E, Gost A, Márquez M; Assessment Research Group in Schizophrenia (NEDES). Gender differences in a sample of schizophrenia outpatients. Compr Psychiatry 2001;42(4):301-305.
30. Addington D, Addington J, Patten S. Gender and affect in schizophrenia. Can J Psychiatry 1996;41(5):265-268.
31. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Third Edition. Washington, DC, American Psychiatric Association, 1987.
32. Carpenter WT Jr. The deficit syndrome. Am J Psychiatry 1994;151(3):327-329.
33. Kirkpatrick B, Buchanan RW, McKenney PD, Alphis LD, Carpenter WT Jr. The Schedule for the Deficit syndrome: an instrument for research in schizophrenia. Psychiatry Res 1989;30(2):119-123.
34. Messias E, Kirkpatrick B, Bromet E, Ross D, Buchanan RW, Carpenter WT Jr, et al. Summer birth and deficit schizophrenia: a pooled analysis from 6 countries. Arch Gen Psychiatry 2004;61(10):985-989.
35. Strous RD, Maayan R, Lapidus R, Stryjer R, Lustig M, Kotler M, et al. Dehydroepiandrosterone augmentation in the management of negative, depressive, and anxiety symptoms in schizophrenia. Arch Gen Psychiatry 2003;60(2):133-141.
36. Andreasen NC, Olsen S. Negative v positive schizophrenia. Definition and validation. Arch Gen Psychiatry 1982;39(7):789-794.
37. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987;13(2):261-276.
38. Owens DG, Miller P, Lawrie SM, Johnstone EC. Pathogenesis of schizophrenia: a psychopathological perspective. Br J Psychiatry 2005;186:386-393.
39. Fenton WS, McGlashan TH, Victor BJ, Blyler CR. Symptoms, subtype, and suicidality in patients with schizophrenia spectrum disorders. Am J Psychiatry 1997;154(2):199-204.
40. Nasrallah HA, Weinberger DR. Neurology of schizophrenia. In: Nasrallah HA, Weinberger DR, editors. Handbook of schizophrenia: I. Amsterdam: Elsevier; 1990.
41. Dollfus S, Petit M. Principal-component analyses of PANSS and SANS-SAPS in schizophrenia: their stability in an acute phase. Eur Psychiatry 1995;10(2):97-106.
42. Edwards J, McGorry PD, Waddell FM, Harrigan SM. Enduring negative symptoms in first-episode psychosis: comparison of six methods using follow-up data. Schizophr Res 1999;40(2):147-158.
42. Malla AK, Norman RM, Takhar J, Manchanda R, Townsend L, Scholten D, et al. Can patients at risk for persistent negative symptoms be identified during their first episode of psychosis? J Nerv Ment Dis 2004;192(7):455-463.
44. Young DA, Zakzanis KK, Bailey C, Davila R, Griese J, Sartory G, et al. Further parameters of insight and neuropsychological deficit in schizophrenia and other chronic mental disease. J Nerv Ment Dis 1998;186(1):44-50.
45. McIntosh AM, Holmes S, Gleeson S, Burns JK, Hodges AK, Byrne MM, et al. Maternal recall bias, obstetric history and schizophrenia. Br J Psychiatry 2002;181:520-525.
46. Buka SL, Goldstein JM, Seidman LJ, Tsuang MT. Maternal recall of pregnancy history: accuracy and bias in schizophrenia research. Schizophr Bull 2000;26(2):335-350.
47. Tel Aviv University. "Are Men The 'Weaker' Sex? Pregnancy With Male Fetus Riskier, Study Claims." ScienceDaily. ScienceDaily, 1 April 2009. www.sciencedaily.com/releases/2009/03/090331112729.htm.
48. Sheiner E. The relationship between fetal gender and pregnancy outcome. Arch Gynecol Obstet 2007;275(5):317-319.
49. Ghindini A, Salafia CM. Gender differences of placental dysfunction in severe prematurity. BJOG 2005;112(2):140-144.
50. Di Renzo GC, Rosati A, Sarti RD, Cruciani L, Cutuli AM. Does fetal sex affect pregnancy outcome? Gend Med 2007;4(1):19-30.
51. Melamed N, Yogev Y, Glezerman M. Fetal gender and pregnancy outcome. J Matern Fetal Neonatal Med 2010;23(4):338-344.
52. Sheiner E, Levy A, Katz M, Hershkovitz R, Leron E, Mazor M. Gender does matter in perinatal medicine. Fetal Diagn Ther 2004;19(4):366-369.
53. Kraemer S. The fragile male. BMJ 2000;321(7276):1609-1612.
54. Ring N, Tantam D, Montague L, Newby D, Black D, Morris J. Gender differences in the incidence of definite schizophrenia and atypical psychosis-focus on negative symptoms of schizophrenia. Acta Psychiatr Scand 1991;84(6):489-496.
55. Gallagher BJ, Bur SA, Jones BJ, McFalls JA, Moss DM. Deficit schizophrenia, gender and social class of origin. J Mens Health 2008;5(5):245-248.
56. Canuso CM, Pandina G. Gender and schizophrenia. Psychopharmacol Bull 2007;40(4):178-190.