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MATERNO-FETAL MEDICINE

Pregnancy and postpartum specifics in women with schizophrenia: a meta-study

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Abstract
Objective This meta-study intends to elucidate schizophrenia–pregnancy inferences.
Methods A total of 63 quasi-randomized, case–control, linkage studies on outcomes of singleton pregnancies in women with schizophrenia are identified through PubMed, ACOG, and SCOPUS. A sample of 216 pregnant and puerperal women with schizophrenia, allocated from studies of level I–IIA evidence, is compared with a sample of 487 births to unaffected women. Calculations use births as unit of analysis. Poisson regression model is used in exchangeable correlation structure.
Results Older age (2.13), excessive smoking (1.85) and less antenatal care (1.92) in women with schizophrenia determine high risk for prematurity (2.08), including miscarriages (2.04) and preterm birth (1.98). Neonates to mothers with schizophrenia are profiled with twice likelihood of low Apgar scores (2.22), intrauterine growth retardation (2.16), and congenital defects (2.1). Poor maternal–fetal attachment and preoccupation about fetus are related to negative symptoms of schizophrenia (−0.518), length of antipsychotic treatment (−0.304) and are not associated with maternal age (0.216). Postpartum period is eventful with psychotic relapse (7.86), and parenting difficulties (11.2).
Conclusions After adjusting for age, parity, unhealthy behaviors, length of antipsychotic treatment, and maternal–fetal attachment, maternal schizophrenia remains predictive to prematurity and postpartum psychosis.

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Introduction

Studies conducted in aftermath of deinstitutionalization suggest a significant increase in pregnancies among women with serious mental illnesses [35, 40, 50, 53]. The incidence and prevalence of perinatal poor outcomes in women with schizophrenia are being controversially reported to be higher [3, 5, 10, 14, 16, 17, 21, 41, 43, 45, 51, 60], or similar to that in general population [6, 29, 33, 56]. The modifying impact of excessive smoking [11, 19, 54], older age [47, 55], unplanned pregnancy [36, 54], low parity [30, 52], exposure to antipsychotics [4, 18, 56], delayed recognition of pregnancy and labor signs [6, 7, 34–36], poor attachment to fetus [2, 9, 22, 27, 30, 45, 49], less prenatal care [5, 6, 25, 51], associative medical conditions [47], and the extent to which pregnancy outcomes are intrinsically related to schizophrenia [59, 62, 63] remain as major themes of debates.

Several studies suggest that schizophrenia and schizoaffective disorders are independent risk factors for congenital malformations [16, 18, 21, 59]. Women with schizophrenia have more unwanted pregnancies, less prenatal care, and reduced likelihood of having a partner or spouse. These are significant disadvantages that compound the risks for mother and child in addition to the direct impact of schizophrenia [12, 39, 57]. Women with prominent negative symptoms and chronic course of schizophrenia have significantly higher rates of obstetrical complications and lower Apgar scores (0–3) than women with prominent positive symptoms [25]. Newborns to mothers with schizophrenia show significantly reduced

arousal—associated with neurological abnormality and deviant sensitivity to stimulation, but not with obstetric complications [47, 48]. Children of women with schizophrenia have higher rates of sudden infant death syndrome (SIDS) [23, 26]. Mothers with schizophrenia and their infants are more likely to have poorer interactions (sensitivity and responsiveness) than mothers with affective disorders and their infants [28, 33].

Other studies suggest that schizophrenia–pregnancy inferences are determined mainly by unhealthy behaviors (smoking, poor diet, less care and connection to fetus) [11]. Pregnant women with schizophrenia are at lower risk of preeclampsia. There are no other differences in the incidence of specific complications, such as placenta previa, placental abruption, and abnormal fetal presentation. There is no significant difference between pregnancy outcomes in women who give birth before and after the onset of schizophrenia. Nevertheless, women with schizophrenia are at an increased risk of in-partum interventions: C-section, vaginal-assisted delivery, amniotomy, and pharmacological induction or augmentation of labor [6, 24].

Postpartum is a time of increased risk for exacerbation of schizophrenia. Negative symptoms of schizophrenia, such as apathy or difficulty expressing emotions, may contribute to under stimulation or neglect of the child, and high rates of custody loss [36, 54]. The absence of formal DSM-IV diagnostic criteria for postpartum psychosis promotes disparate treatment under the law [49]. There are limited data on the use of widely prescribed second generation antipsychotics in pregnant and breastfeeding women with mental disorders. For ethical reasons, research on these subjects mostly relies on collection of single datasets of cases to establish treatment guidelines [27]. Several studies support the use of atypical psychotropics, such as, olanzapine or risperidone, during breast feeding [2, 4, 13, 15, 20]. Authors recommend that the decision to breast feed be made after individual risk–benefit analysis that includes recording severity and frequency of symptoms of maternal mental illness, level of family support, woman's general cooperation with treatment, ability to closely monitor the newborn, understand early warning signs of exposure to antipsychotics in breastfed newborn, and supply the health staff with timely and reliable informants.

Current research on maternal–infant health is replete with discussions on attachment and bonding. Maternal–fetal attachment (MFA) or the "umbilical affect" is about psychosocial commitment of a pregnant woman to her fetus, and the response of the fetus to this commitment [33]. Biologically, the MFA is explained by neuroendocrine interactions and exchanges of catecholamines, including epinephrine, norepinephrine and dopamine [1, 8, 28, 31, 37, 38, 61]. MFA is manifested in behaviors that demonstrate care and commitment to the fetus and include nurture (eating well, abstaining from illicit substances), comforting (stroking the belly), and physical preparation (buying baby clothes and equipment) [7, 32]. The frequency and intensity of MFA behaviors increase with advancing gestational age, particularly after the onset of fetal movements at 18–22 gestational weeks [28, 38]. MFA is consistently related to pregnancy planning, strength of marital relationship, social support, gestational age, and maternal depression and anxiety [45, 46]. From a clinical perspective, approximately 8% of women develop minimal attachment to fetus [44].

Maternal–fetal attachment scale (MFAS) was developed by Cranley [8] and is equipped to quantify 24 items of the following five subscales: role taking, differentiation of self from fetus, interaction with fetus, attributing features to the fetus (fetal image, or physical and kinesthetic awareness of fetus), and giving of self. Condon [7] suggests a 19-item scale of two underlying dimensions: affective experiences (closeness/distance, tenderness/irritation, pleasure in interaction, distress at fantasized loss, conceptualization of the fetus as a 'person') and intensity of preoccupation (amount of time spent thinking about fetus, talking and palpating fetus).

Given the scant discussions on maternal–fetal conflicts (MFC) in the existing obstetrical knowledge, this review classifies the following MFC for their further use as mediators of perinatal adverse outcomes: (1) behavioral/cultural (vegetarian or reduced diet, smoking, informed assent for treatment or termination of pregnancy) [3, 10, 12, 56] (2) psychosocial (serious mental illness, illicit drug use, alcoholism) [7, 28, 35, 38, 57], (3) environmental (informed or uninformed exposure to environmental hazards, such as vibration, chemicals, heavy metals, and bio-hazards), (4) obstetrical (placental defects, such as preeclampsia, uterine fibroids and septum; abnormal placentation—mostly cervical), (5) medical (preexisting diseases [diabetes mellitus, hypertension, thyroid dysfunction, cancer, lupus], vertically transmitted infections [cytomegalovirus, HIV, chlamydia trachomatis, hepatitis C, herpes simplex, active toxoplasmosis, rubella]), (6) biological (Rhesus and LHA conflicts), (7) iatrogenic (diagnostic errors and malpractice) [42, 52], (8) paternal (unwanted pregnancy, financial instability, older age, poor relationships and poor attachment) [58] (9) legal—conflict between legal infrastructures (Supreme Court and State Laws) [14, 24], (10) bioethical (conflicts between Committee Statements, like American Academy of Pediatrics, American College of Obstetricians and Gynecologists) [42].

Sample

Of the 85 retrieved papers, only 63 studies on presentation of schizophrenia in pregnancy and postpartum are eligible according to specific inclusion criteria: singleton pregnancies, and reported statistical power (0.05 maximum alpha level, 95% CI, maximum type II error of 0.80). A sample of 216 pregnant and puerperal women with schizophrenia is selected for exploratory data from studies of levels I–IIA evidence. A sample of 487 births to women without mental illnesses is used for control.

Methods

Studies published between 1977 and 2010 are identified through PubMed, ACOG, PsycINFO and SCOPUS. Results from different reports are combined to produce a pooled odds ratio according to the Mantel–Haenszel method, using both fixed, and random effects models. Pooled estimates of candidate factors, and outcomes from a sample of 216 pregnant and puerperal women with schizophrenia are compared with a sample of 487 births to women without mental illnesses—randomly selected from obstetrical data identified with the help of the same Mesh terms. Maternal–fetal attachment subscales are modeled as process variables to explain factor–outcome relationships.

Factors

A variety of personal, clinical, and behavioral variables are considered in a model to predict perinatal outcomes. Personal characteristics include maternal age, parity, and marital status. Clinical features include gestational age, onset of schizophrenia, its course, antipsychotic treatment, vertical infections, fetal distress, preeclampsia, and intrauterine growth retardation (IUGR). Behavioral factors, include smoking, diet, illicit drug use, number of antenatal visits, and the means of maternal–fetal attachment sub-scales: affective experiences (closeness, tenderness, pleasure in interaction, distress at fantasized loss, conceptualization of fetus as a 'person') and intensity of preoccupation (amount of time spent palpating, interacting with fetus).

Measurable outcomes

Frequencies of binary variables (prevalence and incidence of miscarriages, stillbirth, preeclampsia, abnormal fetal presentation, oligohydramnios, placental abruption and presentation, augmented labor, C-section, obstetrical forceps, small for gestational age newborns, birth defects, sudden infant death syndrome, postpartum psychosis and parenting difficulties) are modeled as outcomes, and odds of numerical variables (Apgar scores, weight/height of the newborn and duration of postpartum psychosis) are used as linear functions exposed to factors.

Data analysis

Calculations use births as unit of analysis. One-way analysis of variance (ANOVA) is used for continuous data; Kruskal–Wallis ANOVA is used for ranked ordinal data; and chi-squared (χ^2) is used where data are categorical. Descriptive statistics are used to profile characteristics of samples. For binary variables, relative risk (RR) and its 95% confidence interval (CI) are computed on an intention-to-treat basis. Continuous data are presented by weighted mean difference statistic, with a 95% CI. For each variable, frequency tables are obtained and distributions examined for the presence of outliers, and missing data. Crude odds ratios with 95% CI not containing unity are followed up by adjusting the OR for maternal age, parity, onset of schizophrenia, and length of antipsychotic treatment. For multivariate models for scored outcomes, generalized estimating equations are used with an exchangeable correlation structure into which a Poisson regression is fitted. Data are analyzed with Epi-Info (version 3.5.1), and ASSISTAT (version 7.5β) programs.

Results

Table 1 profiles the samples. The absent data are marked as missing values (mv): as can be seen in Table 1, mothers with schizophrenia are older (RR 2.13, 95% CI 1.41–2.86), have shorter relationships with partners (OR 0.86, 95% CI 0.64–1.17), are twice likely to smoke (RR 1.85, 95% CI 1.02–2.67), lack in antenatal vitamin intake (RR 1.92, 95% CI), and have higher odds for definite obstetrical complications (RR 2.08, 95% CI 1.04–6.14), including miscarriages (RR 2.04, 95% CI 0.88–1.28), and preterm labor (RR 1.98, 95% CI 0.19–2.79). Newborns to mothers with schizophrenia are profiled with lower Apgar scores (RR 2.22, 95% CI 0.56–8.84), are at twice increased risk for growth retardation (RR 2.16, 95% CI 1.48–3.87), and congenital defects (RR 2.1, 95% CI 1.1–3.8). Postpartum period in women with schizophrenia is characterized with high risk for psychotic relapse (RR 7.86, 95% CI 2.1–17.8), and parenting difficulties (RR 11.2, 95% CI 4.48–23.6). Schizophrenia group is profiled with lower risk for preeclampsia, fetal malposition, and placenta previa (RR 0.81, 0.67, and 0.78, correspondingly). When compared with unaffected mothers, no significant differences are noted regarding stillbirth, precipitate delivery, augmented labor, and non-elective C-section (RR 1.1, 1.22, 1.08, and 0.95,

Table 1 Clinical characteristics of the groups

Category	Baseline: schizophrenia group ($n = 216$)	Adjusted: comparison group		t test T (P) and test for trend χ^2 (P)
		Adjusted OR and RR	95% CI	
Women over 35 years % (N)	14.8 (32)	2.13	1.41–2.86	0.0002
Length of relationships M (SD)	2.98 (1.1)	0.86	0.64–1.17	0.00015
Parity: nullipara % (N)	39.8 (86)	1.11	0.95–1.34	0.0005
Unintended pregnancy % (N)	32.8 (71)	1.17	0.98–1.22	0.0005
Length of antipsychotic treatment M (SD)	10.8 (8.4)	–	–	0.0025
Regular smokers % (N)	29.6 (64)	1.85	1.02–2.67	0.0005
Smoking during pregnancy % (N)	20.8 (45)	1.17	0.86–1.36	0.002
Less vitamin intake in pregnancy % (N)	28.2 (61)	1.92	0.23–2.48	0.0005
PANSS scores				
Prominent positive symptoms M (SD)	24.2 (4.8)	–	–	0.0003
Prominent negative symptoms M (SD)	15.0 (3.4)	–	–	0.0002
MFA				
Quality M (SD)	3.48 (1.2)	0.78	0.15–2.16	0.00036
Preoccupation M (SD	2.56 (1.4)	0.45	0.2–1.36	0.0005
Cumulative number of antenatal visits M (SD)	3.2 (1.2)	0.91	0.66–1.26	0.0012
Miscarriages % (N)	5.1 (11)	2.04	0.88–1.28	0.0008
Stillbirth % (N)	1.85 (4)	1.1	0.98–1.22	0.0006
Preeclampsia % (N)	5.5 (12)	0.81	0.28–2.33	0.00038
Mother-to-child (vertical) infections % (N)	mv	–	–	–
Oligohydramnios % (N)	mv	–	–	–
Fetal malposition % (N)	2.3 (5)	0.67	0.38–1.13	0.0005
Placenta previa % (N)	0.9 (2)	0.78	0.4–1.16	0.001
Preterm labor % (N)	5.09 (11)	1.98	0.19–2.79	0.0006
Precipitate delivery % (N)	8.3 (18)	1.22	0.62–2.42	0.0005
Augmented labor % (N)	6.0 (13)	1.08	0.79–1.64	0.0005
Non-elective C-section % (N)	16.2 (35)	0.95	0.52–1.2	0.0005
Obstetrical forceps % (N)	mv	–	–	–
Low 5-min Apgar scores ($\leq$6) % (N)	6.5 (14)	2.22	0.56–8.84	0.0005
Small for gestational age newborns % (N)	7.4 (16)	2.16	1.48–3.87	0.0003
Birth defects (holoprosencephaly, microcephaly, spina bifida, Down, etc) % (N)	5.09 (11)	2.1	1.1–3.8	0.0018
Sudden infant death syndrome (SIDS) % (N)	6.0 (13)	1.05	0.92–1.22	0.0005
Two or more obstetrical complications % (N)	45.8 (99)	2.08	1.04–6.14	0.0002
Psychotic relapse during pregnancy% (N)	6.9 (15)	3.89	1.04–7.3	0.0005
Psychotic relapse in postpartum (depression, suicidal ideation) % (N)	37.5 (81)	7.86	2.1–17.8	0.0005
Parenting difficulties % (N)	31.0 (67)	11.2	4.48–23.6	0.0005

correspondingly). No data are found on mother-to-child transmitted infections, oligohydramnios, and applications of obstetrical forceps in women with schizophrenia.

Maternal–fetal attachment (MFA) in women with schizophrenia confers lower quality and preoccupation scores (OR 0.78, and 0.45, respectively). Weak negative associations are found between quality of attachment to fetus and length of antipsychotic treatment ($r^2 = -0.304$), as well as with years in partner relationships ($r^2 = -0.298$). Substantial negative associations are found between preoccupation about fetus and negative syndrome-scale ($r^2 = -0.518$). No associations are found between the age of women and quality of attachment, and preoccupation about fetus ($r^2 = 0.216$ and $r^2 = 0.289$, correspondingly).

Figure 1 illustrates citatometric weight of pooled perinatal outcomes and their determinants in reviewed sample:

It is shown that studies are focused on more descriptions of perinatal risk factors to women with schizophrenia

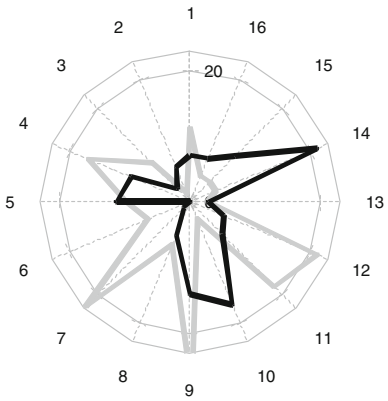

Fig. 1 Weighted presentation of perinatal risk factors and outcomes in reviewed sample

rather than outcomes. Smoking, unintended pregnancy, exposure to antipsychotics, poor maternal–fetal attachment, poor fetal image remain the major themes. Preterm labor, non-elective C-section, small for gestational age (SGA) newborns, low Apgar scores, and postpartum psychosis are the mostly reported outcomes. No data are identified on mother-to-child transmitted infections, oligohydramnios, and applications of obstetrical forceps in women with schizophrenia.

Discussion

In line with previous studies [16, 19, 21, 23, 39, 47, 48, 59, 63], our findings suggest that older age (14.8%, RR 2.13), smoking (29.6%, RR 1.85), and less antenatal vitamin intake (28.2%,RR 1.92) relate to perinatal risk in schizophrenia. Women with schizophrenia confer higher rates of cumulative obstetrical complications (45.8%, RR 2.08), including miscarriages (5.1%, RR 2.04), and preterm labor (5.1%, RR 1.98). The most salient findings in neonates to mothers with schizophrenia are lower 5-min Apgar scores (6.5%, RR 2.22), intrauterine growth retardation (7.4%, RR 2.16), and congenital defects (5.09%, RR 2.1), including holoprosencephaly, microcephaly, spina bifida, and chromosomal syndromes (RR 2.1). Similar findings are reported by Hizkiyahu [16], Nilsson [39], Schneid-Kofmanan [47], Jablensky [21], and others. Postpartum in schizophrenics is specified with high rates of psychotic relapse (37.5%, RR 7.86), and parenting difficulties (31 %, RR 11.2). Consistent with other studies [6, 11], our findings suggest that women with schizophrenia have lower rates of preeclampsia (5.5%, RR 0.81), fetal malposition (2.3%, RR 0.67), and placenta previa (0.9%, RR 0.78). When compared with unaffected mothers, no significant differences are noted regarding stillbirth, precipitate and augmented labor, non-elective C-section, and SIDS.

In line with existing data [25, 33, 43], we found that the quality of maternal–fetal attachment and preoccupation with fetus were not associated with age of women, but were substantially related to the exposure to antipsychotics ($r^2 = -0.304$), marital relationships ($r^2 = -0.298$), and negative symptoms of schizophrenia ($r^2 = -0.518$).

Smoking, exposure to antipsychotics, unintended pregnancies, poor maternal–fetal attachment, poor fetal image were the most discussed themes in studies on maternal schizophrenia. Preterm labor, non-elective C-section, SGA newborns, low Apgar scores, and postpartum psychosis were the mostly met outcomes in studies related to maternal schizophrenia. There were no discussions on vertically transmitted infections, oligohydramnios, and assisted labor with obstetrical forceps in women with schizophrenia in the reviewed literature.

Limitations and strength

Owing to its design, this study enables omit variables: for example, intrauterine growth retardation could be both, cause and consequence of psychotic relapse in pregnancy. Next, a possibility of type II error may exist in studies that do not suggest increased perinatal risks and adverse outcomes. The strength of this study is first in its multidimensional assessments. Secondly, it classifies and prioritizes maternal–fetal conflicts.

Conclusions

Findings of this study inform the following key messages for antenatal care of women with schizophrenia: (1) maternal

schizophrenia is not intrinsically predictive for pre-eclampsia, stillbirth, placenta previa, fetal malposition, augmented labor, non-elective C-section and sudden infant syndrome, (2) older age, less parity, shorter marital relationships, excessive smoking, poor antenatal care are significant disadvantages that compound the risks for mother and child, and determine increased cumulative rate of obstetrical complications (45.8%) in this population, (3) given the complexity of direct and indirect factors affecting pregnancy outcomes in women with schizophrenia, the maternal–fetal attachment scale is helpful in monitoring and measuring indirect perinatal risk factors, and preventing related adverse outcomes. (4) After adjusting for potential confounders women with schizophrenia remain at higher risks for miscarriages (5.1%), preterm birth (5.1%), having newborns with twice lower Apgar scores (6.5%), intrauterine growth retardation (7.4%), and congenital defects (5.09%).

Implications for research

Attesting to the complex and diverse nature of maternal schizophrenia are wide variations in such relevant factors as these: premorbid personality patterns of the patients, their breastfeeding history, onset of illness, types of precipitants which presumably actuate the disease, racial/cultural specifics, level of patient–provider communication, social support, among others. The role of parity, maternal–fetal attachment, maternal–fetal conflicts and their association with negative symptoms of schizophrenia, hold promise for facilitating further research.

Conflict of interest None declared.

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