Case Report

Schizophrenia during Menopausal Transition

Elizabeth A Crow

Assistant Professor, Department of Psychiatry, University of Minnesota, USA

Suzanne Jasberg

Assistant Professor, Department of Psychiatry, University of Minnesota, USA

ABSTRACT

This article is a review of three cases of menopausal transition first episode psychosis that occurred at our institution. Possible explanations for this second wave of schizophrenia during the menopausal transition and early menopause may be from hormonal changes, specifically hypoestrogenism, that can be the catalyst in women with an underlying risk for schizophrenia. Other mental illnesses, such as preexisting unipolar depression and bipolar affective disorder can worsen during menopausal transition. Other hypoestrogenic periods, including postpartum and menstruation, have been shown to have increased risk of psychosis onset or symptom exacerbation for some women. This highlights a possible hormonal connection between menopausal transition and schizophrenia onset. Additionally, the physiologic changes that occur during this period, including hot flushes (vasomotor symptoms) and sleep deprivation may be particular stressors that exacerbate mental illness. Possible women's health interventions may have a particular benefit in women with new onset psychosis during menopausal transition or menopause.

MeSH Headings/Keywords: Schizophrenia; Psychosis; Menopausal transition; Perimenopause; Menopause

Case Report

Case 1

Patient 1 is a 46 year old woman with a past history of depression (diagnosed over a year prior to presentation) who presented to the emergency room with auditory hallucinations, paranoia, and social and vocational decline that was increasing over 9 months. Patient's depression was also worsening despite treatment with citalopram. She was brought in to the emergency room due to paranoid delusions, bizarre behavior, and verbal outbursts related to delusional content. During the interview, she was somewhat disorganized and guarded during initial assessment, not answering many questions. She denied anhedonia, depressed mood, feelings of helplessness or hopelessness, and denied suicidality. She endorsed auditory hallucinations. The patient was admitted for first psychosis work up, which was negative, and stabilized on aripiprazole. Reproductive history showed cessation of menses 1-2 years prior to admission, after myomectomy. Patient was not pregnant, on hormone replacement therapy nor hormonal birth control.

Case 2

Patient 2 is a woman who was first diagnosed at age 50 with her first episode of psychosis. She was then admitted for worsening psychotic symptoms at age 56, where admission differential included bipolar disorder, type 1 with psychosis versus schizoaffective disorder, bipolar type, This presentation was in the setting of medication non-adherence. No mania or depression symptoms were endorsed by the patient. She perseverated on difficulty sleeping, endorsed auditory hallucinations, and appeared to be responding to internal stimuli, during admission. She was prescribed risperidone, which treated her psychotic symptoms. First psychosis workup was presumed negative at outside institution, and reproductive history was not able to be obtained, although patient was not pregnant nor on hormone replacement therapy. Her diagnosis of psychosis at age 50 fits with the early menopausal period.

Case 3

Patient 3 is a 58 y/o woman with 2 months of delusional thinking. According to her family, she was disorganized and unsafe in the home. She called police due to paranoid delusions and requested admission for her safety. She declined medication. She felt that her family was plotting against her and that people were watching her through hospital windows. Her husband reported that when she was entering menopause, she had a very similar episode where she became delusional and paranoid, and acted on delusional content. She was treated at an outside hospital for depression at that time, and stabilized on citalopram. She then was stable without medication for 5 years, until two months prior to this presentation. The result of her hospitalization was civil commitment for psychiatric treatment and olanzapine therapy, which was effective. She declined a first episode workup, and did not offer a reproductive history. The patient was not pregnant nor on hormone replacement therapy.

Introduction

First episode psychosis during the fifth decade of life is not a rare occurrence for women. Our cases exemplify this phenomenon. 37% of schizophrenia in women is diagnosed ages 45-54 [1,2]. Despite this second wave of late onset schizophrenia in women, it can still be quite shocking for the patient and family, as well as for care providers, including psychiatric providers. During menopausal transition, the period of a few years prior to the cessation of menses, both follicle stimulating hormone and estradiol levels drop significantly [3]. Women often seek care from their primary care provider or OB/GYN during this period because of disruptive and often debilitating vasomotor symptoms of menopausal transition [4]. Studies show that women with a history of hormonally associated psychopathology, e.g., peripartum depression or psychosis, or Premenstrual Dysphoric Disorder (PMDD), can be especially vulnerable to recurrent psychopathology during the menopausal transition [5,6]. It should not be forgotten that this

time of "hormonal" vulnerability is also associated with a second wave of women presenting with new onset schizophrenia [7].

Estrogen replacement during the menopausal transition can decrease the stressors associated with hypoestrogenic states, including sleep deprivation from vasomotor symptoms, provide possible neuroleptic effects, and potentially augment neuroleptic therapy [8,9]. Clinical trials looking at estrogen therapy in chronic schizophrenia have primarily looked at younger women or women late in menopause [10]. Although these studies show improvement in psychotic symptoms, they use unopposed estrogen, which would limit potential therapy for women with an intact uterus or those who are still at risk for pregnancy.

Raloxifene, a selective estrogen receptor modulator, may have similar benefit to estrogen in patients with schizophrenia, without direct effects on reproductive tract. This novel approach may allow estrogen modulation to be applied in a broader range of women, perhaps improving psychotic symptoms [11,12].

This article will define menopausal transition, review first psychosis diagnosis and workup, address possible etiological causes of this later wave of schizophrenia in women, and propose possible hormonal therapies in women with menopausal transition first episode psychosis.

Menopausal transition

The menopausal transition period is also known as perimenopause, or climacteric. The transition period takes place for approximately 5-7 years prior to the cessation of menses. The average age of natural menopause is 51-52, so the menopausal transition usually occurs in the mid-40's, with most studies citing age 45 as the beginning of menopausal transition. This can be a vulnerable time for women, especially with a history of mental illness, possibly due to these increased hormonal changes [3,13]. Menopause is defined clinically as the cessation of menses for one year, or the time of surgical menopause (bilateral ovaries removed). FSH greater than or equal to 40 can also indicate menopausal status, if the diagnosis is unclear.

50-82% of women will have vasomotor symptoms of menopause, and 33% of those will have more than 10 hot flushes a day. Vasomotor symptoms are hot flushes or night sweats, which are a sudden onset of heat in the face, neck, and chest lasting one to several minutes. Skin temperature rises because of peripheral vasodilation, with a drop in core body temperature from estrogen withdrawal. These vasomotor symptoms are associated with increased norepinephrine and serotonin release, which lowers the core temperature set point in the hypothalamus. Resolution of these symptoms can take thirty minutes. These symptoms often begin in menopausal transition, and can last up to 10 years. Disruptive and debilitating vasomotor symptoms are the main reason women seek medical care, usually from primary care or OB/GYN, because of menopausal transition [4]. Women with a history of smoking, obesity, depression, anxiety, or low socioeconomic status, are more likely to have vasomotor symptoms [4]. There is data to suggest vasomotor symptomatology has a genetic predilection, thus not all women encounter discomfort during the menopausal transition [14]. The most debilitating result of vasomotor symptoms is sleep disruption and deprivation.

A woman who is experiencing menopausal transition and psychotic symptoms, however, may not acknowledge hot flushes and night sweats, or may be too disorganized or paranoid to provide her reproductive history. As with our cases above, menopausal transition was presumed by the patient's age and history, or from collateral information. All providers, including psychiatrists, should attempt to obtain some reproductive history from a patient, especially if there is evidence that vasomotor symptoms may initiate the onset of or worsen current mental health symptoms, and can be treated. Similarly, primary care providers should be mindful of the substantial number of women with first episode psychotic symptoms in the menopausal time. It is also possible that inquiring about and addressing menopausal symptoms in patients may help curb possible exacerbation in mental health symptoms.

First episode psychosis

Schizophrenia occurs in 1% of the population, and is approximately split evenly between the sexes. In women however, more than a third of cases occur after age 44, while most men are diagnosed with schizophrenia before age 30 [2]. According to the Diagnostic and Statistical Manual of Mental Disorder, Fifth Edition, schizophrenia diagnosis requires two or more of the following symptoms that occur over a 6 months period: 1) delusions, 2)hallucinations, 3) disorganized speech, 4) grossly disorganized or catatonic behavior, 4) negative symptoms. At least one of these symptoms must be 1-3. Negative symptoms include low motivation, reduced affective range, limited socialization, and decreased spontaneous speech. Along with these psychotic symptoms, functioning in major areas like work, self-care, educational achievement (primarily in youth), or personal relationships declines below the patient's baseline, which was evident in our three cases. Other psychopathology should be ruled out, as well as potentially reversible physiologic or substance induced etiology [15] (Table 1).

Reicher-Rossler in 1992 stipulated that the second wave of schizophrenia in women was the same as schizophrenia occurring in their younger male and female counterparts, and hence in this

Table 1: First Psychosis Workup.

First Tier labs/tests	Second Tier labs/tests
Urine pregnancy test	
CBC with differential	Heavy Metal Screen
Comprehensive metabolic panel	Urine porphyrins
	Rheumatologic studies
Urinalysis	Hepatitis panel
Urine drug screen	Adrenoleukodystrophy
Vitamin B12	Other inherited metabolic disorders
Folate	
TSH with reflex FT4	Huntington's disease
Fasting lipids	Di George's syndrome (velocardiofacial syndrome)
HIV	
RPR/Treponemal antibody	Tuberus Schlerosus
EIA	Adult Tay-Sach's or Niemann-Pick's
Ceruloplasmin	
ESR	Paraneoplastic syndrome
ANA	Cognitive screen
Lyme titer	Neuropsychological testing
CXR	Neurology Consult and LP
MRI Head	EEG
EKG	

article we recommend similar diagnostic criteria and therapies, with the possible consideration for the addition of hormone therapy [9]. As was done in 2 of our 3 cases, a first episode psychosis workup is warranted in these patients. A suggested work up is below, addressing other causes of psychosis, that are not due to a primary thought disorder. These may be especially important to rule out in an individual who falls outside of the classic presentation. A comprehensive evaluation would include electrolyte abnormalities, thyrotoxicosis, urinary tract infection, inflammatory causes (e.g., lupus cerebritis), infectious causes (including HIV and neurosyphilis), metabolic causes (e.g., Wilson's disease), and brain lesions or neurodegenerative process. The following laboratory studies may be of interest in determining underlying etiology for presenting symptoms, if clinically applicable, after a history and physical have been obtained.

An FSH could also be added, if the provider is unable to obtain a reproductive history. Typically, a value greater than or equal to 40 would be consistent with menopause, which could allow the provider to consider HRT/ERT as an adjuvant to other treatments.

The duration of untreated psychosis in the United States is approximately two years, which is much longer than other countries. The little data evaluating the duration of untreated psychosis in the postmenopausal women, but one could hypothesize it is even longer. Our cases reflect this.

The RAISE (recovery after initial schizophrenia episode) study, through NIMH (National Institute of Mental Health), has shown that comprehensive first episode care is not only effective but also feasible in our payer system. Ongoing expansion of this model will continue to improve access to care across our nation, with the goal of reduced duration of untreated psychosis and improved long term outcomes [16].

Discussion

Etiology of schizophrenia presenting during menopausal transition

The mechanism for menopausal transition onset schizophrenia is uncertain. Hypoestrogenism seems to be associated with psychotic symptoms, in a subset of women. There may be a mental health diathasis during menopausal transition, seen both in mood disorders such as bipolar disorder with psychosis and primary thought disorders like schizophrenia. Studies link a history of premenstrual syndrome/premenstrual dysphoric disorder and perinatal bipolar illness or depression with a more chronic mental health condition during menopause. A case series of 5 women with bipolar affective disorder and postpartum psychosis demonstrated worsening of symptoms during perimenopause. In these individuals, most presented with psychosis in the setting of an acute manic episode [6]. Sleep deprivation is a major stressor during the menopausal transition, which can exacerbate many mental illnesses [17,18].

Some theories of biologic vulnerability in schizophrenia suggest that estrogen has action at the at the Dopamine D2 receptor, presynaptically, and may increase serotonin 5HT 2a receptor density. Some theories propose that estrogen may have a protective effect, as evidenced by the increase in symptom severity in some women with schizophrenia at the time of menopause [7]. Women with typical onset of schizophrenia tend to have a more mild course compared to their male counterparts, until they enter the menopausal period [2]. There are animal models and clinical reports that suggest that estrogen has an anti-dopaminergic effect, with resultant psychotic symptomatology during low estrogen periods, like after bilateral oophorectomy, post-abortal, menstrual, or after exposure to anti-estrogens, like tamoxifen [19,20].

Estrogen was found to decrease psychotic symptoms in younger premenopausal women with schizophrenia in a meta-analysis done by Begemann in 2011 [10] of 4 small randomized, controlled trials. The authors recommended future trials as their n of 214 was too small for clinical application. The majority of the studies were done by Kulkari, in 2001 [21], 2002 [22] and 2008 [23]. These were all done using unopposed estrogen as an adjunct to neuroleptics over a 28 day period to treat acute psychosis in women with an average age of 32-34(much younger than our cases). Two of the three studies showed statistically significant improvement in psychotic symptoms. This comparison is limited as the patients in these studies were still actively menstruating. However, the clinical improvement shown in these studies is encouraging. Further, a study of combination progestin and estrogen therapy showed no effect on pre-menopausal women with schizophrenia and their relapse rates. This may show that additive progestin possibly negates the beneficial effects of estrogen for mental health, although the numbers of the study were small (n=46) [7]. Lastly, a placebo-controlled, double-blind crossover study with 19 premenopausal women with schizophrenia were found to have improved thought processing after estrogen replacement [24].

Raloxifene, a selective estrogen receptor modulator, was shown to improve memory and executive functioning in menopausal women with schizophrenia (n=33) [11]. Another study of 46 menopausal women with schizophrenia, demonstrated improved positive symptoms when raloxifene was used with risperidone [12]. The benefit of raloxifene over estrogen alone is that raloxifene has estrogenic effects in the brain but not in the breast or endometrium. However, the numbers are still too small to guide clinical decisions. This continues to be an area of study.

Treatment

Treatment of menopausal transition psychosis – family medicine role

Overview: A primary care physician has the benefit of knowing patients over time, appreciating their baseline, and addressing changes. Menopausal transition schizophrenia is not an uncommon occurrence. Thus, recognizing risk factors, revisiting the second "bump" of first episode schizophrenia in women in their 40's, and making appropriate referrals when necessary will be important in managing these patients. Keep in mind that risk factors for menopausal transition schizophrenia include a positive family history, age in the mid-forties, a history of psychosis during a previous low estrogen time (postpartum) and single/widowed/divorced status.

Psychosis intervention: Women who present with psychotic symptoms should be screened to ensure they are not a danger to themselves or others due to disorganization, severity of delusional thought processes, homicidal or suicidal ideation. Next, these women warrant a thorough workup to confirm there is not a condition outside of a primary thought disorder responsible for their altered mental status, as detailed above. Reducing the duration of psychosis improves patients' outcome, thus a timely treatment of symptoms is warranted. Often, these patients are very appropriate referrals to a collaborating psychiatrist. Primary treatment for schizophrenia is antipsychotic medication, but the remainder of the article will address possible hormonal adjunctive therapies. For a more complete discussion of antipsychotic medication, please refer to the EUFEST and CAFE studies [25,26]. Initiating an antipsychotic medication in addition to promoting low stress environments and avoidance of substances of abuse, especially marijuana and stimulants, are recommended in this group.

Should women presenting to your clinic during menopausal transition also have a diagnosis of schizophrenia, HRT may be of dual benefit. Next, this paper will review various treatment strategies for HRT in a primary care clinic.

Hormonal Intervention: Addressing fertility and hormonal changes

Women who have not ceased having menses may still be at risk for pregnancy, and HRT does not prevent unplanned or undesired pregnancy. Antipsychotic medication can also mimic menopause in approximately 50% of women taking it, by increasing prolactin levels, leading to amenorrhea [27]. These women may still have some fertility, despite the amenorrhea. Primary care physicians are well placed to address both the need for contraception and possibly prevention of menopausal transition vasomotor symptoms.

ERT: Women without a uterus

The use of estrogen alone in women without a uterus can reduce vasomotor symptoms of menopause, but has a slight increased risk of venous thromboembolism. The benefits, however, include decreased osteoporosis and colon cancer risks. Contraindications include hypertriglyceridemia (>400 mg/dL), active liver or gallbladder disease, venous thromboembolic disease, coronary heart disease (CHD), breast or GYN cancer. Usual treatments are oral estradiol 1 mg daily or equine estrogen 0.625 mg daily or weekly patch with estradiol 0.05 mg/daily. Additionally, these formulations of estrogen were found to be effective in the studies of women with schizophrenia [21-23].

HRT: Women with a uterus

The need for birth control should be the primary decision point in women with a uterus, which is addressed above. Additionally, when a patient has symptoms of psychosis, other important health care needs often go unaddressed. In patients with psychosis, there is an increased risk of unplanned pregnancy**.** With this risk, there is an increased risk of elective abortion [27], as well as a 3 fold risk of birth defects [28]. If the patient is still menstruating, but with significant vasomotor symptoms, low dose birth control pills, etonogestrel ring or levonogestrel IUD with estrogen replacement therapy are helpful to treat symptoms, provide neuroleptic adjunctive therapy, and provide contraception. Low dose birth control pills, containing 10-20 mcg of ethinyl estradiol, or the contraceptive vaginal ring, are ideal for women requiring contraception. Women in their 40's or younger, who experience surgical or early menopause, will require higher doses of hormones, which would be more physiologic. Low dose birth control may be a viable option for these younger women, even though they no longer require contraception [4]. Gynecologic consult may be needed to decide when to transition women from low dose contraception to hormone replacement.

If the patient is menopausal, hormone replacement can be used to treat vasomotor symptoms, and possibly be adjunctive to neuroleptics. Hormone replacement therapy in women with a uterus should include combination estrogen and progestin. Progestin is necessary to protect the endometrium from unopposed estrogen and endometrial cancer. Progestins can cause fatigue and dysphoria, so dosing at night is advised. Progestins have the same contraindications as estrogen, but can be less thrombogenic. They also were implicated, in the Women's Health Initiative, with slight increased risks of breast cancer and cardiovascular disease. However, this was found primarily in women in their 60's and 70's,who are past the 10 year vasomotor symptom window of menopausal transition and early menopause. There are many formulations of oral and transdermal estrogen/progestin combinations. If dosing progestins as separate from the estrogen, suggestions are Medroxyprogesterone Acetate 2.5 – 5 mg nightly, Progesterone 100 – 200 mg nightly, or the Levonogestrel intrauterine device [4].

Conclusion

Unfortunately, patient's route to care, and long duration of untreated psychosis, represent the current state of first episode access to care in the US. We must continue to improve. They all had substantial duration of untreated psychosis. It is unclear if the psychosis was not apparent to their families and primary care providers, or if psychosis was not included in the differential due to their more mature age of presentation. Lastly, this is often an independent patient population, having had marriages, family and careers. Thus, inherently, psychotic symptoms present with above average psychosocial supports in place. This can be beneficial to this group, compared to the younger cohort of men and women with schizophrenia.

This paper reviewed the phenomenon of late onset schizophrenia in women during menopausal transition. It is important to keep schizophrenia on the differential for women 40's – 50's who present with altered mental status or abnormal thought process. There may be a protective benefit of hormone therapy during the menopausal transition, for vasomotor symptoms and for worsening of other psychiatric symptoms, including depression, mania and psychosis. Research shows that estrogen, and possibly selective estrogen receptor modulators, can be used adjunctively in chronic schizophrenia. Our study population could benefit from more encompassing hormonal treatment. Treatment in this population could range from contraception,estrogen replacement +/- progestin. Coordinating seamless care for these patients will be necessary in order to

augment their treatment, and will often include primary care, OB/GYN, and psychiatry. There remains a relative paucity of information about interventions for this group of women.

There is a need for more studies focusing on women in their mid-40's, who seem to be hormonally vulnerable, and represent the age of the second schizophrenia peak. Menopausal transition is a clinical diagnosis, hence establishing a theoretical age of 45 - 55 would possibly capture at risk women during menopausal transition and early menopause. Selecting a high risk population for schizophrenia development would help further elucidate if hormonal therapy could prevent psychosis. Innovation in estrogen delivery to patients with a mental health diathesis would address safety issues inherent in unopposed estrogen use. It will also be necessary to address risks and benefits of these different regimens in first episode psychosis patients. Differentiating between women with and without a uterus, with and without fertility, and with natural versus surgical menopause, would provide needed information to address patients' different hormone adjuvant needs and possible hormonal adjuvant therapies. As our field moves forward to address the whole patient, primary care, OB/GYN and psychiatry will continue to align.

References

1. Gupta R, Assalman I, Bottlender R. Menopause and Schizophrenia. *Menopause International.* 2012; 18: 10-14.
2. Alyosi A, Van Dyk K, Sano, M. Women's Cognitive and Affective Health and Neuropsychiatry. *Mt Sinai J Med.* 2006; 73: 967-975.
3. Schmidt PJ, Haq N, Rubinow D. A Longitudinal evaluation of the relationship between reproductive status and mood in perimenopausal women. *Am J Psychiatry.* 2004; 161: 2238-2244.
4. Kaunitz AM and Manson JE. Management of menopausal symptoms. *Obstetrics & Gynecology.* 2015: 126: 859-876.
5. Cohen LS, Soares CN, Otto MW, Sweeney BH, Liberman RF, et al. Prevalence and predictors of premenstrual dysphoric disorder (PMDD) in older premenopausal women: The Harvard Study of Moods and Cycles. *J Affect Disord.* 2002; 70: 125-132.
6. Blackmore ER, Craddock N, Walters J, Jones I. Is the perimenopause a time of increased risk of recurrence in women with a history of bipolar affective postpartum psychosis? A case series. *Arch Womens Ment Health*. 2008; 11: 75-78.
7. Bergemann N, Mundt C, Parzer P, Pakrasi M, Eckstein-Mannsperger U, et al. Estrogen as an adjuvant therapy to antipsychotic does not prevent relapse in women suffering from schizophrenia: results of a placebo-controlled double-blind study. *Schizophr Res*. 2005; 74: 125-134.
8. Riecher-Rossler A, Hafner H. Schizophrenia and oestrogens - is there an association? *Eur Arch Psychiatry Clin Neurosci.* 1993; 242: 323-328.
9. Riecher-Rossler A, Loffler W, Munk-Jorgensen P. What do we really know about late-onset schizophrenia? *Eur Arch Psychiatry Clin Neurosci.* 1997; 247: 195-208.
10. Begemann MJH, Dekker CF, van Lunenburg M, Sommer IE. Estrogen augmentation in schizophrenia: A quantitative review of current evidence. *Schizophr Res*. 2012; 141: 179-184.
11. Huerta-Ramos E, Iniesta R, Ochoa S, Cobo J, Miquel E, et al. Effects of raloxifene on cognition in postmenopausal women with schizophrenia: A double-blind, randomized, placebo-controlled trial. *Eur Neuropsychopharmacol.* 2014; 24: 223-231.
12. Kianimehr G, Fatehi F, Hashempoor S, Khodaei-Ardakani MR, Rezaei F, et al. Raloxifene adjunctive therapy for postmenopausal women suffering from chronic schizophrenia: a randomized double-blind andplacebo controlled study. *Daru.* 2014; 22: 1-7.
13. Parry B. Perimenopausal Depression. *Am J Psychiatr.* 2008; 165: 23-27.
14. Rebbeck TR, Su HI, Sammel MD, Lin H, Tran TV et al. Effect of hormone metabolism genotypes on steroid hormone levels and menopausal symptoms in a prospective population-based cohort of women experiencing the menopausal transition. *Menopause.* 2010; 17:1026-1034.
15. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th Edition: DSM-5. Washington, DC: American Psychiatric Publishing; 2013.
16. Kane JK, et al. The Raise early treatment program for first-episode psychosis: Background, rationale, and study design. *J Clin Psychiatry.* 2015; 76: 240-246.
17. Harlow BL, Cohen LS, Otto MW, Spiegelman D, Cramer DW. Prevalence and predictors of depressive symptoms in older premenopausal women. The Harvard study of moods and cycles. *Arch Gen Psychiatry.* 1999; 56: 418-424.
18. Riecher-Rossler A. Oestrogens and schizophrenia. *Curr Opin Psychiatry.* 2003; 16: 1-13.
19. Harlow BL, Wise LA, Otto MW, Soares CN, Cohen LS. Depression and its influence on reproductive endocrine and menstrual cycle markers associated with perimenopause. The Harvard study of moods and cycles. *Arch Gen Psychiatry.* 2003; 60: 29-36.
20. Mahe V, Dumaine A. Oestrogen withdrawal associated psychoses. *Acta Psychiatrica Scandinavica.* 2001; 104: 323-331.
21. Kulkarni J, Riedel A, De Castella AR, Fitzgerald PB, Rolfe TJ, el al. Estrogen - a potential treatment for schizophrenia. *Schizophr Res.* 2001; 48: 137-144.
22. Kulkarni J, Riedel A, De Castella AR, Fitzgerald PB, Rolfe TJ, et al. A clinical trial of adjunctive oestrogen treatment in women with schizophrenia. *Arch Womens Ment Health.* 202; 5: 99-104.
23. Kulkarni J, de Castella A, Fitzgerald PB, Gurvich CT, Bailey M, et al. Estrogen in severe mental illness. *Arch Gen Psychiatry.* 2008; 65: 955-960.
24. Bergemann N, Parzer P, Jaggy S, Auler B, Mundt C, et al. Estrogen and comprehension of metaphoric speech in women suffering from schizophrenia: Results of a double-blind, placebo-controlled trial. Schizophr Bull. 2008; 34: 1172-1181.

25. Fleischhacker WW, Keep IP, Kahn RS, et. al. The european first episode schizophrenia trial (EUFEST): rationale and design of the trial. *Schizophr Res.* 2005; 78: 147-156.

26. McEvoy JP, Lieberman JA, Perkins DO, Hamer RM, Gu H, et al. Efficacy and tolerability of olanzapine, quetiapine, and risperidone in the treatment of early psychosis: a randomized, double-blind 52-week comparison. *Am J Psychiatry.* 2007; 164: 1050-1060.

27. Bursalioglu FS, Aydin N, Yazici E, Yazici AB, et al. The Correlation Between Psychiatric Disorders and Women's Lives. *J Clin Diagn Res.* 2013; 7: 695-699.

28. Coughlin CG, et al. Obstetric and Neonatal Outcomes After Antipsychotic Medication Exposure in Pregnancy. *Obstetrics & Gynecology*. 2015; 125: 1224-1234.

Address for Correspondence: Elizabeth A Crow, Assistant Professor, Department of Psychiatry, University of Minnesota, Minneapolis, USA, Tel: 612-273-9824; E-mail: ande0395@umn.edu

Submitted 09 Feb, 2016
Accepted 05 May, 2016