Gender Differences in the Presentation and Management of Social Anxiety Disorder

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Social anxiety disorder is associated with significant impairment in social and occupational functioning. Gender differences in social anxiety disorder are apparent for treatment seeking and symptom clusters, and hormonal influences may affect the natural course of illness. The lifetime prevalence rate is 13.3%, with rates of 15.5% in women and 11.1% in men. Although most studies indicate that more women suffer from social anxiety disorder, it appears that men are more likely to seek treatment. Gender differences in the presentation and management of social anxiety disorder may be influenced by fluctuations in levels of endogenous or exogenous reproductive hormones. Neurotransmitter systems implicated in the etiology of mood and anxiety disorders may be affected by both estrogen and progesterone. There are also issues with regard to pregnancy in women who have social anxiety disorder. It is not known if untreated social anxiety disorder represents a significant risk to the fetus. However, social anxiety disorder often is complicated by comorbid depression, panic disorder, or substance abuse, all of which may pose risks to the fetus if left untreated. Treatment strategies for patients with social anxiety disorder should consider gender differences in response to pharmacotherapy, psychiatric comorbidity, oral contraceptive use, pregnancy status, and the specific nature of symptoms in the individual patient. *(J Clin Psychiatry 1999;60[suppl 9]:9–13)*

Social anxiety disorder is the most common anxiety disorder and is associated with significant impairment in social and occupational functioning. As in many mood and anxiety disorders, including major depression and panic disorder, the prevalence of social anxiety disorder is higher in women than in men. However, unlike in major depression and panic disorder, little attention has been paid to the issue of gender differences in social anxiety disorder. The existing literature regarding gender differences in the presentation and management of social anxiety disorder and factors that may contribute to such differences will be explored here.

PREVALENCE

Two epidemiologic studies have described lifetime and 12-month prevalence data for social anxiety disorder. The Epidemiologic Catchment Area (ECA) study indicated that the lifetime prevalence of social anxiety disorder is 2.4%, with a higher prevalence in females (3.1%) than males (2.0%) (Figure 1).[1] Data from the National Comorbidity Survey (NCS) also indicate that prevalence rates are higher in women than in men. An overall lifetime prevalence rate of 13.3% was reported, with a rate of 15.5% in women compared with 11.1% in men.[2] The large difference in lifetime prevalence rates between the 2 studies is thought to be due to the use of diagnostic criteria from the DSM-III (*Diagnostic and Statistical Manual of Mental Disorders, Third Edition*) in the ECA study and DSM-III-R criteria in the NCS study. The DSM-III-R criteria permitted patients with a generalized avoidance of social situations to be included in the diagnosis of social anxiety disorder. In DSM-III, these patients were classified as having avoidant personality disorder and were excluded from a diagnosis of social anxiety disorder. In addition, the NCS study used the Composite International Diagnostic Interview to elicit information. This diagnostic instrument is more thorough than the Diagnostic Interview Schedule used in the ECA study, particularly for social anxiety disorder.[2] The NCS study more accurately describes the true prevalence of social anxiety disorder, demonstrating that it is the most common anxiety disorder and the third most common psychiatric disorder, exceeded in lifetime prevalence only by major depression (17.1%) and alcohol dependence (14.1%).[2]

It is clear that women are more likely to have social anxiety disorder. However, men are more likely to seek treatment. Two studies have indicated that at social anxiety dis-

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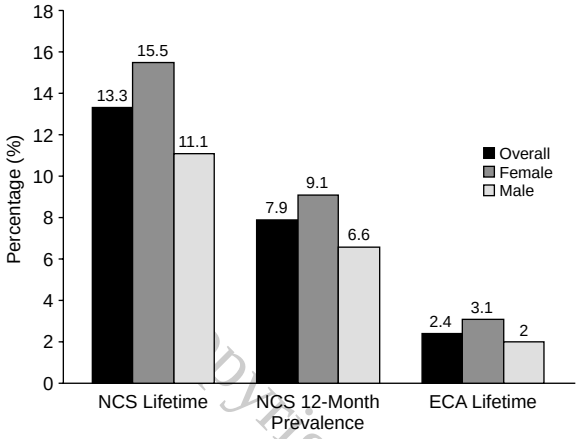
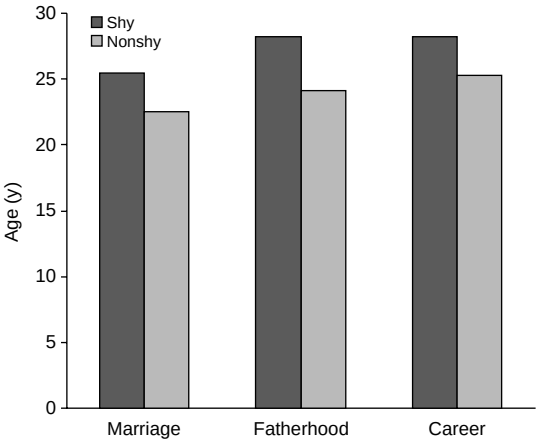
Figure 1. Prevalence of Social Anxiety Disorder by Gender in 2 Large Epidemiologic Studies[a]



[a]Data from references 1 and 2. Abbreviations: ECA = Epidemiologic Catchment Area study, NCS = National Comorbidity Survey.

Figure 2. Social, Parental, and Occupational Transitions in 24 Shy Versus 63 Nonshy Males[a]



[a]Adapted from reference 6, with permission.

order clinics there is an equal or slightly higher preponderance of males.[3,4] This difference may be in part due to differences in levels of distress experienced by men and women with social anxiety disorder. Pollard and Henderson[5] found that, although the ratio of women to men who fit criteria for social anxiety was 3:2, when diagnostic criteria included "significant distress," the ratio was 2:3. However, only 2% of subjects were classified as "distressed"; therefore, this result may not be clinically significant.

Differences in gender roles and social expectations may explain why men with social anxiety disorder tend to seek treatment more often than women. In most Western cultures, males have been expected to be more assertive and outgoing in social interactions. In contrast, women traditionally have been encouraged to take a more passive role. Thus, when symptoms of social anxiety disorder interfere with the ability to interact with others and perform in work, school, or social settings, these symptoms may affect men more severely than women. Data from studies of shyness are consistent with this theory. In one study of life-course patterns of shy children, shy boys and girls were followed into adulthood.[6] Males who were judged to be shy in childhood appeared to suffer more social and occupational dysfunction as adults than their female counterparts. Shy males married and had their first child 3 or more years later than nonshy males ($p < .01$) (Figure 2), but this was not the case for shy females. Shy males also entered a steady career 3 years later than nonshy males ($p < .05$). In contrast, shy females were less likely to ever work outside the home or reenter the workforce after marriage or childbirth than their nonshy female counterparts ($p < .05$).

Other studies of childhood shyness validate a gender effect. Bacon and Ashmore[7] reported that shyness in boys is associated with more negative feedback from parents and peers than shyness in girls. Mills and Rubin[8] reported that sons are more likely to be admonished by parents for shy, inhibited behavior than are daughters. Although childhood shyness differs from social anxiety disorder, the 2 conditions share some characteristics, including difficulty with social interactions. Thus, the differential effect on social and occupational functioning seen between shy men and women in adulthood may explain the increased treatment-seeking seen in men with social anxiety disorder when compared with women with the disorder.

CHARACTERISTICS OF SOCIAL ANXIETY DISORDER

There appear to be gender differences in the situational and performance fears associated with social anxiety disorder as well. Pollard and Henderson[5] evaluated point-prevalence rates and demographic differences for 4 common performance fears associated with social anxiety disorder: public speaking or performing, writing in front of others, eating in restaurants, and use of public restrooms. The overall rate of social anxiety disorder was higher in women, but concerns about eating in restaurants and writing in public were more common in men. However, problems with using public restrooms and speaking or performing in public were more common in women (Figure 3).

Response to Psychotherapy

The issue of gender differences in response to psychotherapy, specifically cognitive-behavioral therapy (CBT), is a newly emerging field of study, with major depression among the first psychiatric disorders to be studied. However, few data exist regarding gender differences in response to CBT or other psychotherapeutic interventions in patients with social anxiety disorder. This is an area that requires further study.

Figure 3. Differential Rates of 4 Common Performance Fears Among Men and Women With Generalized Social Anxiety Disorder[a]

[a]Data from reference 5.

ENDOCRINE INFLUENCES

Although existing data are from preclinical models and must be extrapolated to clinical situations, fluctuations in levels of endogenous reproductive hormones may contribute to gender differences in the presentation and management of social anxiety disorder. Both estrogen and progesterone have been shown to affect neurotransmitter systems implicated in the etiology of mood and anxiety disorders. Estrogen increases the density of dopamine receptors when applied to striatal neurons in the rat[9,10] and has been shown to inhibit monoamine oxidase activity.[11] The effects of estrogen on dopamine may explain the second peak of onset of schizophrenia in women, but not men, older than 40 years of age.[9] There are also complex interactions between estrogen and serotonin systems. Estradiol administration in female rats causes acute increases in 5-HT_{2A} receptor density in the cerebral cortex and nucleus accumbens.[12] Progesterone metabolites have been shown to act on GABA receptors in a manner similar to benzodiazepines and barbiturates.[13–15]

Endogenous Hormones

There have been reports of symptom worsening in association with normal fluctuations in levels of endogenous reproductive hormones during the menstrual cycle in women with panic disorder or obsessive-compulsive disorder (OCD). For example, in a study by Williams and Koran,[16] 42% of women with OCD reported premenstrual exacerbation of OCD symptoms. Women with panic disorder have also retrospectively reported worsening of symptoms during the luteal phase of the menstrual cycle, although prospective ratings have failed to demonstrate worsening of panic in a number of small studies.[17–19] Whether this phenomenon also exists in women with social anxiety disorder is unknown.

Exogenous Hormones

Exogenous hormones can also affect pharmacotherapeutic response in women with social anxiety disorder. Depression and irritability have been associated with oral contraceptive use in women without underlying psychiatric disorders.[20] Both the estrogen and progestin components of these contraceptives have been implicated as the causal factor in mood disturbance, although most researchers feel that the mood disturbances are secondary to the synthetic progestin component.[21]

Oral contraceptives can interfere with both pharmacokinetic and pharmacodynamic responses to psychotropic medications. They are hepatically metabolized and can increase clearance of compounds metabolized by conjugation and glucuronidation and decrease clearance of compounds metabolized through oxidation.[22] In addition, drugs that increase hepatic enzyme induction may increase metabolism of oral contraceptives, leading to subtherapeutic levels and contraceptive failure.[23]

Few data exist regarding potential interactions between oral contraceptives and selective serotonin reuptake inhibitors (SSRIs), β-blockers, or monoamine oxidase inhibitors (MAOIs). Theoretically, estrogen-dominant oral contraceptives can decrease serum levels of benzodiazepines that undergo glucuronidation, such as lorazepam, oxazepam, and temazepam. In addition, they can increase serum levels of benzodiazepines that undergo oxidation, such as alprazolam, triazolam, diazepam, and chlordiazepoxide.[24,25] The response to diazepam may fluctuate across the menstrual cycle in women taking oral contraceptives. The estrogen component of the oral contraceptives may affect absorption of diazepam, leading to differences in serum levels during the 3 weeks of contraceptive use versus the hormone-free week.[26] In patients with social anxiety disorder, attention should be paid to concomitant use of oral contraceptives and benzodiazepines. In some cases, an adjustment in the dosage of the benzodiazepine may be necessary.

PREGNANCY

Women with psychiatric disorders who wish to become pregnant are faced with difficult decisions regarding the use of psychotropic medications. A number of different issues must be addressed. Risks of fetal exposure to medications, including congenital anomalies, neurodevelopmental sequelae, and perinatal syndromes, must be weighed against the risks of untreated maternal disorder.[27]

There is no evidence to suggest that untreated social anxiety disorder represents a significant risk to the fetus. However, social anxiety disorder often is complicated by comorbid depression, panic disorder, or substance abuse, all of which may pose risks to the fetus if left untreated. In addition, women with untreated severe social anxiety disorder may be hesitant to visit a physician because of anxi-

ety associated with the interaction and therefore may not receive adequate prenatal care. Thus, these potential risks must be weighed against the risks associated with medication exposure during pregnancy.

β-Blockers

Although β-blockers do not have a role in the treatment of generalized social anxiety disorder, they may be used on an as-needed basis for patients with a fear of public speaking. Most of the data regarding safety of β-blockers during pregnancy have addressed use of β-blockers in the treatment of hypertension, not anxiety disorders. Theoretically, β-blockers could cause increased uterine contractions, although this has not been reported as a problem when they have been used during pregnancy. One study reported altered fetal lung development in rats exposed to β-blockers in utero.[28] However, 2 studies conducted in women reported conflicting results. In one study of very low birth weight infants, 7 of 19 infants born to mothers treated with β-blockers during pregnancy died within 1 year of birth, compared with no deaths in 16 infants whose mothers were treated with other antihypertensives.[29] In contrast, in a study of β-blocker use in 121 patients who had 125 high-risk pregnancies, there was no evidence of low Apgar scores or bradycardia in the infants.[30]

Benzodiazepines

Some early reports of benzodiazepine use during pregnancy suggested that first-trimester exposure may be associated with an increased risk of oral clefts.[31–33] However, other studies failed to exhibit such an association.[34,35] Unfortunately, there are a limited number of studies addressing this relationship, and the existing studies utilized a number of different designs. A recent meta-analysis of studies assessing risk of prenatal benzodiazepine exposure suggested that if there is an increased risk of development of oral clefts associated with benzodiazepine use during pregnancy, absolute risk is considered to be low at less than 1%.[36] Further large-scale studies are needed to address this issue. There have been reports of perinatal sequelae associated with in utero exposure to benzodiazepines, including low Apgar scores, failure to feed, neonatal apnea, muscular hypotonicity, and impaired temperature regulation.[37–40] Limited data exist regarding effects of in utero exposure to benzodiazepines on neurodevelopment. Some studies suggest developmental delays,[41,42] whereas others do not.[35]

Monoamine Oxidase Inhibitors

Monoamine oxidase inhibitors are effective in the treatment of social anxiety disorder.[43–45] However, in utero exposure to MAOIs has been associated with an increased risk of congenital anomalies in humans[46] and neurologic abnormalities in animals. In addition, use of MAOIs is contraindicated with terbutaline, a medication often used to manage premature labor.

Selective Serotonin Reuptake Inhibitors

The SSRIs have been well studied in pregnancy. A number of studies have suggested that in utero exposure to fluoxetine is not associated with an increased risk of major malformations.[47,48] A registry containing more than 1500 cases of prenatal exposure to fluoxetine failed to show increased rates of congenital anomalies.[36] A preliminary study of neurobehavioral functioning in children exposed to fluoxetine in utero also failed to show adverse effects associated with prenatal exposure to the drug.[49]

Data regarding safety of the other SSRIs are similar, but less extensive. Kulin and colleagues[50] matched 267 women who took paroxetine, sertraline, or fluvoxamine during pregnancy with an equal number of controls. There were a total of 222 live births, including 9 major malformations, in women who had taken SSRIs, and 235 births and 9 major malformations in controls ($p = .91$). The rates of miscarriage and stillbirth were similar in both groups, and mean birth weight and gestational age were also similar. Based on these data, paroxetine, sertraline, or fluvoxamine did not appear to increase the risk of congenital anomalies when used during pregnancy. However, given the low overall number of patients followed in this study, more data are necessary to confirm that these drugs do not harm the developing fetus. An additional small study of 63 infants exposed to paroxetine during the first trimester failed to show evidence of congenital anomalies.[51]

The shorter half-lives of paroxetine, sertraline, and fluvoxamine make these SSRIs a better choice for treating a patient who does not wish to take medication during pregnancy but who is not yet pregnant. Since fetoplacental circulation is established 18 to 21 days after conception, a patient who has regular menstrual cycles has a "window" of 4 to 7 days after the first day of a missed menstruation before fetoplacental circulation is established. Thus, such a patient may elect to remain on an SSRI with a short half-life while trying to conceive. She could discontinue the SSRI on the day of missed menstruation, and theoretically the medication would be cleared before fetoplacental circulation was established. Thus, the different SSRIs can be used in different scenarios depending on the severity of psychiatric illness and the situation of the patient.

CONCLUSION

In conclusion, gender differences in the presentation and management of social anxiety disorder can be influenced by both psychosocial and biological factors. Treatment strategies for patients with social anxiety disorder should consider gender differences in response to pharmacotherapy, comorbidity, oral contraceptive use, pregnancy status, and the specific nature of symptoms in the individual patient.

Drug names: alprazolam (Xanax), chlordiazepoxide (Librium and others), diazepam (Valium and others), fluoxetine (Prozac), fluvoxamine (Luvox), lorazepam (Ativan and others), oxazepam (Serax and others), paroxetine (Paxil), sertraline (Zoloft), temazepam (Restoril and others), terbutaline (Brethine), triazolam (Halcion).

REFERENCES

1. Schneier FR, Johnson J, Hornig CD, et al. Social phobia: comorbidity and morbidity in an epidemiologic sample. Arch Gen Psychiatry 1992;49: 282–288
2. Kessler RC, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Comorbidity Survey. Arch Gen Psychiatry 1994;51:8–19
3. Rapee RM, Sanderson WC, Barlow DH. Social phobia features across the DSM-III-R anxiety disorders. J Psychopathol Behav Assess 1988;10: 287–299
4. Solyom L, Ledwidge B, Solyom C. Delineating social phobia. Br J Psychiatry 1986;149:464–470
5. Pollard CA, Henderson JG. Four types of social phobia in a community sample. J Nerv Ment Dis 1988;176:440–445
6. Caspi A, Elder GH, Bem DJ. Moving away from the world: life-course patterns of shy children. Dev Psychol 1988;24:824–831
7. Bacon MK, Ashmore RD. How mothers and fathers categorize descriptions of social behavior attributed to daughters and sons. Soc Cogn 1985;3: 193–217
8. Mills RSL, Rubin KH. Social factors in the development of social withdrawal. In: Rubin KH, Asendorpf JB, eds. Social Withdrawal, Inhibitions, and Shyness In Childhood. Hillsdale, NJ: Erlbaum; 1993:117–148
9. Di Paolo T. Modulation of brain dopamine transmission by sex steroids. Rev Neurosci 1994;5:27–42
10. Häfner H, Riecher-Rössler A, An Der Heiden W, et al. Generating and testing a causal explanation of the gender difference in age at first onset of schizophrenia. Psychol Med 1993;23:925–940
11. Chakravorty SG, Halbreich U. The influence of estrogen on monoamine oxidase activity. Psychopharmacol Bull 1997;33:229–233
12. Fink G, Sumner BEH, Rosie R, et al. Estrogen control of central neurotransmission: effect on mood, mental state, and memory. Cell Mol Neurobiol 1996;16:325–344
13. Kroboth PD, McAuley J. Progesterone: does it affect response to drug? Psychopharmacol Bull 1997;33:297–301
14. Majewska M. Neurosteroids: endogenous bimodal modulators of the GABA-A receptor mechanism of action and physiological significance. Prog Neurobiol 1992;38:379–395
15. Majewska M, Harrison N, Scwartz R, et al. Metabolites of steroid hormones are barbiturate-like modulators of the aminobutyric acid receptors. Science 1986;232:1004–1007
16. Williams KE, Koran LM. Obsessive-compulsive disorder in pregnancy, the puerperium, and the premenstruum [CME]. J Clin Psychiatry 1997;58: 330–334
17. Cameron OG, Kuttesch D, McPhee K, et al. Menstrual fluctuation in the symptoms of panic anxiety. J Affect Disord 1988;15:169–174
18. Cook BL, Noyes R, Garvey MJ, et al. Anxiety and the menstrual cycle in panic disorder. J Affect Disord 1990;19:221–226
19. Stein MB, Schmidt PJ, Rubinow DR, et al. Panic disorder and the menstrual cycle: panic disorder patients, healthy control subjects, and patients with premenstrual syndrome. Am J Psychiatry 1989;146:1299–1303
20. Kendler KS, Martin NG, Heath AC, et al. A twin study of the psychiatric side effects of oral contraceptives. J Nerv Ment Dis 1988;176:153–160
21. Janowsky D, Halbreich U, Rausch J. Association between ovarian hormones, other hormones, emotional disorders and neurotransmitters. In: Jensvold M, Halbreich U, Hamilton J, eds. Psychopharmacology and Women: Sex, Gender, and Hormones. Washington, DC: American Psychiatric Press; 1996:85–106
22. Teichmann AT. Influence of oral contraceptives on drug therapy. Am J Obstet Gynecol 1990;163:2208–2213
23. Fazio A. Oral contraceptive drug interactions: important considerations. South Med J 1991;84:997–1002
24. Abernethy D, Greenblatt D, Shader R. Imipramine disposition in users of oral contraceptive steroids. Clin Pharmacol Ther 1984;35:792–797
25. Abernethy D, Greenblatt D, Divoll M, et al. Impairment of diazepam metabolism by low-dose estrogen-containing oral contraceptive steroids. N Engl J Med 1982;306:791–792
26. Ellinwood EH Jr, Easler ME, Linnoila M, et al. Effects of oral contraceptives on diazepam-induced psychomotor impairment. Clin Pharmacol Ther 1984;35:360–366
27. Cohen LS, Rosenbaum JF. Psychotropic drug use during pregnancy: weighing the risks. J Clin Psychiatry 1998;59(suppl 2):18–28
28. Petit KP, Nielsen HC. Chronic in utero β-blockade alters fetal lung development. Dev Pharmacol Ther 1992;19:131–140
29. Kaaja R, Hiilesmaa V, Holma K, et al. Maternal antihypertensive therapy with β-blockers associated with poor outcome in very-low birthweight infants. Int J Gynaecol Obstet 1992;38:195–199
30. Dubois D, Petitcolas J, Temperville B, et al. β-Blocker therapy in 125 cases of hypertension during pregnancy. Clin Exp Hypertens [B] 1983;2:41–59
31. Aarskog D. Association between maternal intake of diazepam and oral clefts [letter]. Lancet 1975;2:921
32. Safra MJ, Oakley GP Jr. Association between cleft lip with or without cleft palate and prenatal exposure to diazepam. Lancet 1975;2:478–480
33. Saxén I, Saxén L. Association between maternal intake of diazepam and oral clefts [letter]. Lancet 1975;2:498
34. Crombie DL, Pinsent RJ, Fleming DM, et al. Fetal effects of tranquilizers in pregnancy [letter]. N Engl J Med 1975;293:198–199
35. Hartz SC, Heinonen OP, Shapiro S, et al. Antenatal exposure to meprobamate and chlordiazepoxide in relation to malformations, mental development, and childhood mortality. N Engl J Med 1975;292:726–728
36. Altshuler LL, Cohen L, Szuba MP, et al. Pharmacologic management of psychiatric illness during pregnancy: dilemmas and guidelines. Am J Psychiatry 1996;153:592–606
37. Fisher JB, Edgren BE, Mammel MC, et al. Neonatal apnea associated with maternal clonazepam therapy: a case report. Obstet Gynecol 1985;66 (suppl):34S–35S
38. Mazzi E. Possible neonatal diazepam withdrawal: a case report. Am J Obstet Gynecol 1977;129:586–587
39. Rementeria JL, Bhatt K. Withdrawal symptoms in neonates from intrauterine exposure to diazepam. J Pediatr 1977;90:123–126
40. Whitelaw AGL, Cummings AJ, McFadyen IR. Effect of maternal lorazepam on the neonate. BMJ 1981;282:1106–1108
41. Laegreid L, Olegård R, Conradi N, et al. Congenital malformations and maternal consumption of benzodiazepines: a case-control study. Dev Med Child Neurol 1990;32:432–441
42. Viggedal G, Hagberg BS, Laegreid L, et al. Mental development in late infancy after prenatal exposure to benzodiazepines: a prospective study. J Child Psychol Psychiatry 1993;34:295–305
43. Gelernter CS, Uhde TW, Cimbolic P, et al. Cognitive-behavioral and pharmacological treatments of social phobia: a controlled study. Arch Gen Psychiatry 1991;48:938–945
44. Liebowitz MR, Schneier F, Campeas R, et al. Phenelzine vs atenolol in social phobia: a placebo-controlled comparison. Arch Gen Psychiatry 1992; 49:290–300
45. Versiani M, Nardi AE, Mumdim FD, et al. Pharmacotherapy of social phobia: a controlled study with moclobemide and phenelzine. Br J Psychiatry 1992;161:353–360
46. Heinonen OP, Slone D, Shapiro S. Birth Defects and Drugs in Pregnancy. Littleton, Mass: Publishing Services Group; 1977
47. Chambers CD, Johnson KA, Dick LM, et al. Birth outcomes in pregnant women taking fluoxetine. N Engl J Med 1996;335:1010–1015
48. Pastuszak A, Schick-Boschetto B, Zuber C, et al. Pregnancy outcome following first-trimester exposure to fluoxetine (Prozac). JAMA 1993;269: 2246–2248
49. Nulman I, Rovet J, Stewart DE, et al. Neurodevelopment of children exposed in utero to antidepressant drugs. N Engl J Med 1997;336:258–262
50. Kulin NA, Pastuszak A, Sage SR, et al. Pregnancy outcome following maternal use of the new selective serotonin reuptake inhibitors: a prospective controlled multicenter study. JAMA 1998;279:609–610
51. Inman W, Kubotu K, Pearce G. Prescription event monitoring of paroxetine. Prescription Event Monitoring Rep 1993:1–44