Depressive and anxiety disorders are highly comorbid during the perinatal period. Women with histories of these disorders are at risk for relapse during pregnancy and the postpartum (1). At least one in every ten pregnant women fulfills diagnostic criteria for depression (2). Untreated mood and anxiety disorders in the perinatal period have serious consequences. They have direct effects on foetal, obstetric, neonatal outcomes and also have long term neurodevelopmental effects. The use of antidepressants is a cause of concern for physicians and their patients because of risks of teratogenicity, neonatal toxicity and long term behavioral effects. Selective serotonin reuptake inhibitors (SSRIs) are the mainstay of pharmacological treatment for both depression and anxiety disorders. It is critical to weigh the risks and benefits of exposing the fetus or baby to maternal illness against the risks and benefits of exposure to psychotropic medications in the perinatal period. Advising women on appropriate treatment options in this period poses a particular challenge to clinicians. All psychotropic medications cross the placenta and enter breast milk (3).

Teratogenicity: Most data related to antidepressants in pregnancy are derived from the use of SSRIs (4). There were two reports about a 1.5-2 fold increased risk of congenital cardiac malformations associated with first-trimester paroxetine exposure that have raised concerns and caused the manufacturer to change the drug’s pregnancy FDA category from C to D. One of the two large case-control studies examining the teratogenic effects of SSRIs found no significant associations between SSRI use overall and congenital heart defects; but revealed an association with anencephaly, craniosynostosis, and omphalocele, with a small absolute risk (5). In contrast, the other study showed no increase in risk of craniosynostosis, omphalocele, or heart defects associated with SSRI use (6). There was only an association between paroxetine and right ventricular outflow defects and between sertraline and omphalocele and cardiac septal defects. However, these two studies were limited by the small number of exposed infants for each malformation. Hence, the current data on SSRI exposure during early pregnancy provide conflicting data on the risk for both overall and specific malformations. Although some researchers have found a small increase in the risk of cardiac defects, specifically with paroxetine exposure, the absolute risk is small; therefore these agents are not considered major teratogens. A meta-analysis reported that SSRIs do not increase the risk of major malformations, cardiovascular malformations, or minor malformations but that they do increase the risk of spontaneous abortions (7). Malm et al. suggested that exposure to fluoxetine and paroxetine in early pregnancy is associated with a small but established risk of specific cardiovascular anomalies; fluoxetine is associated with isolated ventricular septal defects (0.5% absolute risk increase) and paroxetine is associated with right ventricular outflow tract defects (0.2% absolute risk increase) (8). Further studies are needed also to clarify whether these risks are attributable to medications, to underlying psychiatric illness, or to other confounding factors.

Neonatal toxicity: SSRIs may produce toxicity or withdrawal effects in the newborn (3). FDA warnings regarding SSRI related withdrawal syndrome in neonates have caused great alarm and discontinuation of pharmacotherapy. With exposure to SSRIs late in pregnancy, transient neonatal complications, including jitteriness, mild respiratory distress, tachypnoea, weak cry and hypotonia were reported (9). Neonatal abstinence syndrome is reported in about 30% of neonates exposed to SSRIs in late
pregnancy, compared to 6% and 9% in neonates with no exposure or early exposure in utero, respectively (10). A recent study reported that not the timing but the length of SSRl exposure increased the risk of respiratory distress as well as lower birth weight and gestational age (11). Poor neonatal adaptation has been also associated with severity of maternal illness (12). More recently, FDA warned about the risk of an unconfirmed association of newborn persistent pulmonary hypertension (PPHN) with SSRl use. In a large case-control study it was found that, although the absolute risk is small, exposure to SSRls in the latter half of pregnancy increased the relative risk of PPHN; but this study did not account for the effect of maternal illness (13).

Breastfeeding: Breastfeeding has clear benefits for both mother and infant. These benefits should be weighed against the risks of medication exposure to the neonate. Studies regarding SSRI use and lactation have shown that medication exposure during lactation is considerably lower than transplacental exposure during gestation. Generally, very low levels of SSRls are detected in breast milk. Only a few isolated cases of adverse effects have been reported, although infant follow-up and long-term neurobehavioral data are limited (14). Measuring serum levels in the neonate is not recommended. However, breastfeeding should be ceased if a nursing infant develops abnormal symptoms most likely associated with exposure to the medication. It is best to prescribe a medication for which safety data exist in breastfeeding and to use the lowest effective dose. In prescribing psychiatric medications to nursing mothers, it is also important to consider the infant’s age. Supplementation with bottle-feeding may reduce the infant’s exposure to the drug. The practice of discarding breast milk when the medication is expected to peak in breast milk can limit the degree of infant exposure to medications. The literature focusing on SSRls in nursing indicates that most infants can continue to nurse without risk of adverse events.

Conclusion

Untreated maternal mental illness has consequences, not only for the mother but also for the developing fetus, the infant, and the child or adolescent. No treatment decision is risk-free: the baby is exposed, either to the medication or to the effects of maternal illness itself. Medication use in pregnancy and postpartum is controversial. Pharmacologic treatment of perinatal mood and anxiety disorders needs careful risk-benefit analysis. The long-term effects of exposure to either medications or maternal mental illness are unknown. Most of negative findings related to SSRI use in pregnancy have not taken into account important variables such as maternal illness and concurrent medication use. Data on alternative therapies, particularly psychotherapies, are not adequate to recommend them as first-line treatments, especially for severely mentally ill women with persisting and relapsing illnesses.

Treatment with a single medication in lowest effective dose, with medication for which safety data exists in pregnancy and breastfeeding is warranted. Most women taking antidepressants during pregnancy are receiving suboptimal doses of their medication. While there are no published data on optimal antidepressant dosing during pregnancy and no studies specifically discussing efficacy of antidepressants during pregnancy, American Psychiatric Association Practice Guidelines recommends flexible dosages for patients with major depressive disorder. The choice of medication should be guided primarily by its safety data and by the patient’s psychiatric history (history of drug efficacy, prior exposure during pregnancy) and severity of symptoms. Optimally, shared decision making among clinicians and the patient should occur before pregnancy. Patients should be presented with up to date knowledge, be engaged in decision making, and closely monitored regardless of their choice of treatment. The risks and benefits may change over the course of treatment and should therefore be re-examined periodically. Informed consent regarding the risks and benefits of exposing the fetus and the newborn to a psychotropic agent and maternal illness must be documented. Treatment should be individualized and multidisciplinary approach is necessary.

References