Psychotropic Drugs in Pregnancy and Breastfeeding: Weighing the Iatrogenic Risks for the Mother-Infant Pair with the Risks Associated with an Untreated Maternal Disorder

Unfortunately, pregnancy and puerperium are not protective against the onset or recurrence of psychiatric disorders.

Concordant information drawn from scientific literature has also demonstrated that antenatal and puerperal mental problems impact severely on the physiological progress of pregnancy, the developing fetus, the infant, and even the future psychological and neurocognitive development of their offspring.

Hence, focusing our attention more closely on perinatal psychiatry may be an effective strategy for reducing the prevalence of psychiatric disorder. In the light of the impact of untreated maternal mental disorder on children's mental health, treating mentally-ill women safely and effectively may reduce the risk of future compromise in their offspring's psychological development. Obviously, effective treatment of maternal mental disorder does not reduce the genetic risk of suffering from mental problems. However, as genetic predisposition acts in conjunction with specific external influences, restoring a healthy family environment may reduce future risk of developing mental problems during adolescence and young adulthood.

Briefly, it would also be useful to remember that maternal depression may complicate pregnancy progression by increasing the probability of unhealthy life-styles and inadequate self-care, both of which lead to an increase in the risk of fetal and placental anomalies, pre-eclampsia, and antepartum bleeding. Impaired intrauterine growth has been also associated with the occurrence of depressive symptoms during the gestational period. Moreover, antenatal depression induces significant effects on neonatal physiology: elevated cortisol and norepinephrine levels, lower dopamine levels, and greater relative right-frontal electroencephalographic asymmetry. All have been reported in infants born to mothers who suffered from mood disorders while pregnant [1]. Such infants are also likely to show depressive-like behaviors [2].

The impact of untreated bipolar disorder on expecting mothers and their fetuses is also likely to be devastating. Indeed, maternal bipolar disorder is associated with an increased frequency of birth defects, perinatal mortality, preterm birth, low birth weight/Apgar scores, and different typologies of perinatal complications, whose occurrence is facilitated by the difficulty of these mothers to adhere to healthy lifestyle changes [3]. Infants born to bipolar mothers are also at increased risk of developing emotional problems, impairments in affective/behavioral responses and social functioning, deficits in spatial memory and attention, as well as suffering from various psychiatric disorders during childhood (preschool offspring of parents with bipolar disorder have an elevated risk for ADHD and have greater levels of subthreshold manic and depressive symptoms), adolescence, or young adulthood [4, 5].

Women with schizophrenia are significantly more likely to have placental abruption, to give birth to newborns in the lowest weight/growth decile, and to have children with cardiovascular congenital anomalies [6].

This background justifies a special journal issue focused on assembling up-to date information on the safety of pharmacological management of antenatal and puerperal psychiatric disorders. Indeed, this information may help clinicians to balance the potential risks for the fetus and the newborn (associated with exposure to psychotropic medications through placenta and/or maternal milk) with the ascertained detrimental effects of untreated maternal mental illness.

An interesting update of Australian epidemiological data about the prevalence of schizophrenia in female patients is provided by McCauley-Elsom, Elsom, and Cross, who also discussed the repercussion on fertility of the increasing use of atypical antipsychotics.

Unfortunately, however, no psychotropic agents seem to be totally devoid of risks for the developing fetus and the neonate.

Although Carlos De las Cuevas and Emilio J. Sanz report in this issue that only a few studies have shown a slight increase in the presence of malformations associated with prenatal use of antidepressants, and that such data are not fully concordant, reviewed literature information conversely demonstrate that late in utero exposure to all classes of antidepressants is likely to induce a spectrum of neonatal complication which resembles, to some extent, the profile of adverse events that such medications may induce in adult patients [7]. Recently, the whole spectrum of neonatal associated with late pregnancy exposure

to antidepressants has been labeled "Prenatal antidepressant exposure syndrome" [8]. However, as reported by Jan Øystein Berle and Olav Spigset, antidepressant treatment does not contraindicate breastfeeding. This reassuring information may facilitate the pharmacological approach of women who develop postpartum depression [9, 10].

Christina Wichman is forced to conclude that, at this time, available data are still insufficient to confirm or exclude a potential structural teratogenic risk associated with intrauterine exposure to both typical and atypical antipsychotic agents, despite being reported elsewhere that there is more reassuring published information regarding typical antipsychotics and, especially, chlorpromazine [11]. Moreover, all antipsychotic agents are likely to induce neonatal adverse reactions if used during late pregnancy [12]. On the other hand, Jacques Dayan, Rozenn Graignic-Philippe, and Gwenaelle Andro, following a comprehensive review of pertinent scientific literature, conclude that, for some of the antipsychotics (haloperidol, risperidone, and quetiapine), there are no signals of adverse effect in the suckling infant. Hence, it is confirmed that the possibility exists that mothers who need antipsychotic medications during puerperium may safely breastfeed their own babies [13].

As regards mood stabilizing agents, our Spanish colleagues rightly highlight that available evidence indicates that, at therapeutic serum levels, lithium poses only a small (albeit measurable) structural teratogenic hazard to human reproduction. Moreover, it appears that the risk of lithium-induced serious adverse events in the breastfed infant is relatively low. The risk of major structural malformations is conversely significantly increased by exposure to either carbamazepine or valproate, whereas it seems negligible during exposure to lamotrigine. All these three antiepileptic drugs show anecdotal information regarding their use during late pregnancy or by lactating women. However, as reported by Angelika Wieck, the high serum levels of lamotrigine in breastfed infants and the theoretical risk of severe skin reactions has lead national guidelines to advise against breast feeding during medication with this drug.

Regrettably, apart from reassuring results regarding antidepressants [14] (which, however, require urgently further confirmation [15]) and worrying results regarding valproate, [16, 17] the potential impact of prenatal exposure to most psychotropic drugs on the infant's later neurodevelopment remains substantially unknown.

Given these considerations, we are forced to completely turn upside-down our approach to pharmacological treatment of mental disorders during pregnancy and puerperium. Clinicians should abandon any attempt to individuate the safest option, and should re-channel their attention toward individuating the least worrying option, since it is irresponsible to leave severely mental ill women untreated, even if pregnant or lactating. However, whatever the choice, obtaining a full informed consent, warranting careful gynecologic monitoring, ensuring that delivery happens in hospitals equipped with Neonatal Intensive Care Units, and providing strict pediatric surveillance of infants up to school age are all indispensable tools for optimizing maternal treatment and reducing the risks for the fetus and the newborn as much as possible.

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