New mood stabilizers and reproductive cycle

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Nuevos eutimizantes y ciclo reproductivo

Summary

Introduction. *The use of new mood stabilizers in the treatment of bipolar disorder has supposed a revolution, especially due to its more favorable profile in many aspects. Nevertheless, therapeutic decisions on treatment during pregnancy and the breastfeeding period are still being debated. Since these new anticonvulsants appeared in the last decade, less naturalistic experience in its use exists during these periods than with other older anticonvulsants.*

Methods. *A Medline and Embase search was conducted from 1970 to 2003 to review the articles published on the use of the new mood stabilizers during pregnancy and breastfeeding, and its effects on contraception. Neurology and psychiatry text chapters and abstracts of the Annual Meeting of the American Psychiatric Association (years 2001-2003) were also reviewed.*

Results. *Although some recent articles suggest that new mood stabilizers could have a smaller risk of congenital defects, and therefore could be used with smaller risks in women in fertile age, most of articles reviewed indicate that there is not enough knowledge on the safety of the new mood stabilizers in pregnancy and breastfeeding.*

Conclusions. *The risks and benefits of continuing with the new mood stabilizers during pregnancy and breastfeeding must be weighed carefully and the severity of the disease and the previous answer to treatment should be taken into account.*

Key words: *Pregnancy. Breastfeeding. Mood stabilizers. Contraception. Bipolar disorder.*

Resumen

Introducción. *La utilización de los nuevos eutimizantes en el tratamiento del trastorno bipolar ha supuesto una revolución, especialmente debido a su perfil más favorable en muchos aspectos; sin embargo, las decisiones terapéuticas acerca del tratamiento durante la gestación y el período de lactancia siguen siendo controvertidas. Dado que estos nuevos anticonvulsivos aparecieron en la década de 1990, existe menos experiencia naturalística en su uso durante la gestación que con otros anticonvulsivos más antiguos.*

Métodos. *Se efectuó una búsqueda bibliográfica en Medline y Embase desde 1970 hasta 2003, para localizar los artículos publicados en torno a la utilización de los nuevos eutimizantes en la gestación y lactancia y a sus efectos sobre la anticoncepción. También se revisaron capítulos de textos de neurología y psiquiatría y los resúmenes de los años 2001-2003 de la Reunión Anual de la Asociación Americana de Psiquiatría.*

Resultados. *Aunque algunos estudios de publicación reciente sugieren que los nuevos estabilizantes podrían poseer un menor riesgo de defectos congénitos, y por tanto podrían ser usados con menores riesgos en mujeres en edad fértil, la mayoría de los artículos revisados coinciden en señalar que no existen conocimientos suficientes acerca de la seguridad de los nuevos eutimizantes en la gestación y en la lactancia.*

Conclusiones. *Los riesgos y beneficios de continuar con los nuevos estabilizantes durante los períodos de gestación y lactancia deben ser sopesados cuidadosamente, y debería tenerse en cuenta la gravedad de la enfermedad y la respuesta previa al tratamiento.*

Palabras clave: *Gestación. Lactancia. Estabilizantes del estado de ánimo. Anticoncepción. Trastorno bipolar.*

INTRODUCTION

Except for the known risk that the depression can become worse in the post-partum period[1,2], there is little evidence on the effects of pregnancy in the natural history of mental disease. Successive studies have presented varied theories during successive studies. It has been suggested that some mental disorders remain stable without treatment during pregnancy[3,4] and that this period can reduce the risk of acute psychiatric disease and protect against recurrences of psychotic disorders, major depression, bipolar disorder and suicide[5,6]. However, there are no conclusive data since psychiatric disorders during pregnancy have not been studied extensively[7].

Bipolar disorder is characterized by a chronic and cyclic course, with numerous remissions and exacerbations. An especially complicated situation on the preventive and therapeutic level is that of women in the

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reproductive age. The menstrual cycle, pregnancy, puerperium, breastfeeding and menopause can noticeably influence the course of this disorder[8]. Investigations on the repercussions of pregnancy on bipolar disorder have also not been conclusive, but rather provide contradictory results[9]. On the one hand, a protective effect of pregnancy has been attributed against recurrences of bipolar disorder. Thus, some authors find that women diagnosed of type I bipolar disorder experience a noticeable decrease in mood disorders during pregnancy, both in terms of frequency as well as duration of the recurrences. This could have important implications on the follow-up of women with risk of recurrences[10]. On the contrary, other studies have considered it a period of risk for relapses, especially after the discontinuation of mood stabilizer treatment[11-13]. Unfortunately, there is not much information on the safety and efficacy of the treatments in case of maintenance during pregnancy in bipolar disorder or the repercussions in case of it being withdrawn[14]. As a consequence of this lack of similarity of criteria, the tendency continues to be to avoid prescribing psychiatric drugs during pregnancy. On the other hand, one of the periods of greatest risk of relapse in women with bipolar disorder is puerperium[8] and the decision on the use of the drug treatment during the breast feeding period is still being debated.

In general lines, it can be stated that drug treatment of bipolar disorder has undergone a revolution over the last years, especially due to the growing use of new mood stabilizers. Drugs used in neurology as anticonvulsants are being included in clinical trials, showing beneficial effects on the different phases of bipolar disorder and in the prevention of relapses. Compared with the conventional mood stabilizers, the new ones present a more favorable pharmacokinetic profile, minimum interactions or much weaker ones and greater tolerability, especially in the cognitive field. As they appeared in the last decade, there is less naturalistic experience in their use during pregnancy than with other older anticonvulsants. While the classical ones are considered potentially teratogenic in humans, the effects of the new ones are not well known up to now. Some studies suggest that the new anti-epileptics may have less risk of congenital defects and thus that these substances could be used with less risk in child-bearing aged women[15]. In general, it is considered that the new mood stabilizers may offer advantages to epileptic women in reproductive years[16], so that these findings could be extended to bipolar women. In regards to the question on whether the new mood stabilizers mean an advance in the treatment of these patients during puerperium, several aspects must be considered. Maternal milk is considered as the best and only nutritive requirement necessary for the newborn during the first six months of life[17]. Positive effects such as a nutritional advantages or protection against infections, together with psychological benefits such as reinforcement of mother-child bond have been well documented[18,19], although there are obvious disadvantages such as the excretion of the medication with the consequent exposure of the newborn and in the case of bipolar women, the harmful effects of the disruption of maternal sleep patterns[20].

On the other hand, since the relationship between bipolarity and post-partum affective disorders was described for the first time in 1970, finding that the risk of relapse in puerperium in bipolar women who had suffered post-partum affective psychosis previously was 50 %[21], many studies have demonstrated extreme vulnerability to relapse in the puerperium period in these women[22,23]. One study found that the number of hospitalizations per bipolar disorder during pregnancy only accounts for three quarters of those that are produced during the non-pregnancy periods; however, during the first post-partum month, hospitalizations were eight times more common, and from the second to twelfth month, they were twice the normal ones[24]. It was found in one study recently published by Freeman[13], in which 50 women diagnosed of bipolar disorder were included that the affective symptoms worsened during the pregnancy in half of them and this deterioration was predictive of the post-partum episodes. Although there have been many explanations for the high morbidity during this period, no plausible theory on it has been demonstrated as of yet. The percentage of bipolar women who will suffer mania or depression in the post-partum ranges from 40 % to 70 %[25]. It is important to keep in mind that this percentage would decrease to 10 % with mood stabilizing prophylaxis[26,27]. Thus, some authors consider that the risk of recurrence in puerperium may be reduced in these women by using prophylaxis with lithium in the last phase of pregnancy or after[28,27]. Although there are no studies that specify the possible long term effects of exposure to anticonvulsants in maternal milk, review articles on the possible cognitive effects and on the behavior of children who were treated with these drugs suggest that most do not experience clinically important effects[29]. Thus, considering the risks associated to an untreated bipolar episode both for the mother as well as the newborn, the use of puerperal prophylaxis with mood stabilizers is advisable for bipolar women during this risk period. However, the use of most of the psychodrugs and pharmacological interventions during breastfeeding is still under debate and the clinical decisions are complicated due to the lack of definitive therapeutical guidelines and literature about it that is most made up of specific cases (table 1).

Thus, it must still be determined if these new drugs really mean an advance in the treatment of bipolar pregnant women. In this article, we have reviewed the data from studies published on the use of third generation anticonvulsant drugs in the pregnancy and breast-feeding period until the present moment, as well as their effects on contraceptive treatment.

METHODS

A search was performed in Medline and Embase from January 1970 to August 2003. The search terms were

TABLE 1. Obstacles in the studies of the use of the new mood stabilizers in breast-feeding

Information based on single cases or short term studies
Studies in multiple drug therapy
Lack of knowledge on the clinical importance of small concentrations in the maternal milk
Difficulties to differentiate potential toxic effects of these drugs, of concomitant diseases in the child

pregnancy, breastfeeding, lactation, mood stabilizers, gabapentin, topiramate, lamotrigine, oxcarbazepine, vigabatrin, levetiracetam and zonisamide. Additional articles were located through the references of the articles obtained. Text chapters on neurology and psychiatry and the abstracts of the years 2001-03 of the Annual Meeting of the American Association of Psychiatry were also reviewed.

RESULTS

Although this review was especially aimed at new generation mood stabilizers, it is important to stress that the recently published articles contribute novelties in regards to the use of a traditionally contraindicated drug, such as lithium, during pregnancy, due to its high teratogenic power. However, the risk of congenital malformations after intrauterine exposure to lithium carbonate does not seem to be as important as previously believed. The risk of Ebstein's anomaly, a congenital malformation of the tricuspid valve, has been the reason to avoid lithium during the pregnancy period for many decades, although it is likely that the potential for this effect is quite inferior to that originally believed[30]. On the other hand, a high risk of relapse and affective instability is detected after the discontinuation of this drug[31,32]. Recently, some authors continue to mention that lithium should be considered as a first line therapeutic option in pregnancy and that, given that the safety of the new stabilizing agents continues to be limited, these should be avoided[9].

When we analyzed the studies published, we found several obstacles (table 2). Given the probable inherent teratogenic risk, clinical trials prior to the marketing of a drug systematically avoid the inclusion of child-bearing aged women who do not use a reliable contraceptive method. In spite of this, recent trials advocate the free decision of the patient, who should assume the decision to participate in the trial, after being informed on the potential risks versus the possible therapeutical benefits[33]. The new antiepileptics: gabapentin, lamotrigine, topiramate, oxcarbazepine, zonisamide, tiagabine and levetiracetam have been classified by the American Academy of Pediatrics and by the FDA within category C (teratogenicity in human fetuses cannot be excluded), although the information existing on the effect of pregnancy in humans comes from preclinical studies on small and selected samples, analyzed by the industry.

TABLE 2. Obstacles in the studies of use of the new mood stabilizers in pregnancy

Systematic exclusion of child-bearing aged women
Selected samples, of reduced size, analyzed by the pharmaceutical industry
Studies in epileptic patients published in neurology journals
Patients with multiple drug therapy with difficulty to define the teratogenic effects of each drug
Variable rates in the general population, which makes comparison difficult

Information on the teratogenic power of the new mood stabilizers continues to be very limited[34,35]. Most of the data on the teratogenicity of the anticonvulsants appear in neurology journals, since they have been obtained from patients with epilepsy and they collect a minimum number of cases, those studying the effects on women with bipolar disorder being very inferior in number. Usually, the cases analyzed follow multiple drug therapy treatment, with several anti-epileptics and other concomitant treatments. Thus it is more difficult to draw valid and individualized conclusions for each drug, which means a new confounding factor and added difficulty to define the teratogenic effects of each drug. On the other hand, comparison with the general population is complicated since the spontaneous abortion rates published vary greatly, ranging from 13 % to 62 %[36].

In the following, we present the main publications on the new mood stabilizers and their influence in the female reproductive cycle.

Gabapentin

Gabapentin was initially developed as a structural analogue of GABA, but it does not directly interact with its receptors. Its exact action mechanism is unknown, although it may be related with increase in activity of this neurotransmitter or with inhibition of the glutamate activity[37]. Preclinical studies suggest potential fetotoxicity (delay has been described in ossification, hydronephrosis and/or increase in the percentage of hydroureters, together with an elevated capacity for fetal loss after implantation in rats)[38,39]. A study has recently been published in epileptic women that collected prospective and retrospective data of 51 fetuses, including 3 twin pregnancies, of mothers who took gabapentin during pregnancy; a total of 44 babies were evaluated. According to the results (table 3), complications rates such as cesareans, abortions, low birth weight and malformations were inferior or similar to those seen in the general population or among women with epilspsy, and the malformation cases appeared in cases of polytherapy[40]. In addition, no congenital anomalies were found in the 11 children born to epileptic women who were treated with gabapentin during the first quarter of pregnancy

TABLE 3. Studies of exposure to gabapentin during pregnancy

Author	*No of pacients exposed*	*Diagnosis*	*Teratogenicity*
Wilton, 2002	11	Epilepsy	No
Montouris, 2003	51	Epilepsy	Single drug therapy: no Multiple drug therapy One case: hypospadia* One case: monorenal patient** One case: minor malformation of auditory canal***

* Multiple drug therapy with gabapentin. ** Multiple drug therapy with phenobarbital. *** Multiple drug therapy with lamotrigine.

from an observational study that included 3,100 epileptic patients that was performed in England[41]. In general, it has been considered that its use in pregnant women should be avoided due to the lack of information on its terotogenic potential[42], reserving it for those cases in which the potential benefit in the mother justifies the probable risk for the fetus[43].

In regards to the interactions with contraceptives, it does not interfere with them and does not modify the endogenous levels of the steroid hormones[16].

No data has been published on exposure to gabapentin during breastfeeding. There is a series of unpublished cases performed by the laboratory. In this study, blood, urine and milk samples were analyzed for six women treated with 4̸0 mg of gabapentin. One woman was incapable of producing milk. In the other five, the amount of gabapentin in the maternal milk was approximately equivalent to those of the maternal levels[20]. Caution is recommended when administering gabapentin to mothers while they are breastfeeding their children[43], and it is also recommended to monitor the child for possible adverse effects such as sedation and suckling problems[44].

Topiramate

In its action mechanism, the selective blocking of the glutamate receptor, GABA potentiation, carbonic anhydrase inhibition and calcium antagonist action are combined[45]. The data published have been on isolated cases (table 4̸). Craniofacial and skeletal malformations have been described in animals in relationship with a decrease in fetus weight[39] that would be similar to the effects observed with acetazolamide and other carbonic anhydrase inhibitors. These effects were not dose related, so that other factors could be involved or be specific to the species. A recent article found transient respiratory distress and suckling problems in four children, two of them premature, exposed to topiramate during pregnancy (prior to conception and during at least the first three months of pregnancy)[46]. A study based on the observation of five births of mothers treated with topiramate in which none of the children presented adverse effects suggests considerable placental passage, although it is indicated that the newborn would have an elevated capacity to eliminate it[47]. Although intrauterine exposure to anti-epileptic drugs has been associated with neuropsychological dysfunction in school aged children and adolescents[48], studies performed in animals with topiramate have not shown adverse effects on learning capacity or on behavior. On the other hand, together with carbamazepine and oxcarbazepine, the metabolism of oral contractive increases and their effectiveness decreases[16,49]. Data on the possible teratogenic effects of topiramate in humans can still not be specified until adequate studies are performed. As with other anticonvulsants, metabolism of ethinyl estradiol and progestogen increase, decreasing the effectiveness of contraceptives[50].

TABLE 4. Studies of exposure to topiramate during pregnancy

Author	*No of pacients exposed*	*Diagnosis*	*Teratogenicity*
Cissok, 2002	4̸	Epilepsy	Transient respiratory distress Sucking problems
Ohman, 2002	5	Epilepsy	No

At present, there is no information published on exposure to topiramate in lactation in humans. There is evidence that it passes through the milk in rats[38,20]. The pharmocokinetics of this drug during pregnancy and lactation in newborns of epileptic mothers has been analyzed, finding an extensive passage through the maternal milk, so that children should be monitored until more information is available[47]. In this same study, it was mentioned that maternal milk would have some minimum concentrations of topiramate, but no adverse effects were observed in the children.

Lamotrigine

Lamotrigine is probably the best studied mood stabilizer within the new ones[51]. It acts through several action mechanisms that include inhibition of voltage dependent sodium channels, inhibition of presynaptic release of excitatory amino acids such as glutamate and aspartate, and antagonism of the calcium and sodium channels. It can also block 5-HT3 serotoninergic receptors and acts by potentiating dopaminergic transmission[52].

Although it is a relatively new anticonvulsant, data are available on its use during pregnancy from a prospective, naturalistic study of exposure in the first quarter performed by the laboratory that markets it[53]. This laboratory (Glaxo-Wellcome) has created a registry of the patients who have received treatment with lamotrigine during pregnancy that is up-dated every 6 months to ana-

lyze possible teratogenic risks associated with the premature use of this drug, especially in the first quarter. Up to March 2003, the data of 593 registries of pregnancy had been analyzed. In treatment with lamotrigine as single drug therapy during the first quarter, the risk of malformations found was 3%. These percentages do not differ from those data mentioned in recent literature for women with epilepsy who received other anti-epileptic drugs in single drug therapy (4%)[54] (table 5). Thus, the authors conclude that the proportion of children who are born without congenital disorders is similar to that expected in the general population or in untreated epileptic women. The same findings are described in other clinical series, both in exposure to lamotrigine prior to pregnancy as well as exposure in different quarters[55,56]. Domínguez describes a group of 40 epileptic patients receiving single drug therapy with lamotrigine who continued with this treatment as single drug therapy with lamotrigine after becoming pregnant, together with folic acid. None of the children presented any major or minor malformation[57]. There are cases described of treatment in combined therapy, which makes it difficult to draw generalized conclusions, for example, that of a child born from a pregnancy in which the mother was receiving treatment with lamotrigine and valproic acid who presented aplasia of the muscle of the lower lip and asymmetrical abduction of the hip. The same study found respiratory distress and apnea-bradycardia in multiple drug therapy with lamotrigine and clobazam and respiratory distress and thrombocytopenia in single drug therapy with lamotrigine[46]. Another publication presents the case of a child born with dysmorphic traits associated to the karyotype 47XXX (delay in intrauterine growth, hypertelorism, cleft palate and septal defect, among other abnormalities) after the mother had been treated with 1,800 mg/day of valproic acid and 100 mg/day of lamotrigine during pregnancy, but it was not possible to elucidate if there was a cause-effect relationship or if it was a coincidence[58]. In this way, some authors conclude that the studies performed do not make it possible to obtain definitive conclusions on the lamotrigine valproic acid combination and their teratogenic effects[59]. Several studies with lamotrigine have been carried out in rats, finding that there was a decrease in the fetal concentrations of folic acid in rats[39], so that the use of folic acid supplements should be considered in all the childbearing aged women who are taking it[60], although these antifolate effects have not been observed in humans. Other analyses have assessed its effect on the organogenesis in rats, finding a decrease in weight at birth, increase in cerebral volume and diameter and ventricular dilation[61]. Pharmacokinetic and pharmacodynamic properties have also been analyzed. Plasma levels of lamotrigine decrease as the pregnancy progresses because its clearance increases[62,63]. These variations are superior to those presented with most of the anti-epileptics, so that there is a sudden decrease at the beginning of the pregnancy and increase after delivery, with differences in each case; thus each patient should be assessed individually[15]. Therefore the importance of monitoring concentrations and performing dose adjustments[64], at least monthly, is indicated in case of using this mood stabilizer during pregnancy[65]. In regards to the transplacental passage, lamotrigine crosses the placenta rapidly and easily, which indicates that the maternal treatment supposes a considerable fetal exposure[66].

On the other hand, lamotrigine does not interfere with contraceptives and does not modify the endogen levels of steroid hormones[16].

Articles that review the literature comparing the teratogenic potential of lamotrigine in relationship with old anti-epileptics conclude that it could offer advantages because it is metabolized by glucuronidation and it is not known that it induces the hepatic cytochrome P450 system or that it forms active metabolites, and in addition, its capacity of binding to proteins is considerably inferior to that of the old anti-epileptics. Thus, although little data still exist, it is possible that it has pharmacokinetic and pharmacodynamic properties that mean a safer profile for its use in pregnancy[67].

The American Academy of Pediatrics designates lamotrigine as a drug with an unknown effect in infants[68]. A considerable amount of lamotrigine is excreted in maternal milk[69], since it has been found that blood levels in the mother may reach approximately 60% and in the fetus 25% to 30% of the maternal levels. Several cases of infants exposed to this drug have been described. In one of them, the mother was treated with lamotrigine at the end of the pregnancy and during breast-feeding; the child was follow-up for five months in the post-partum, observing that the amounts were equivalent to those that are found after therapeutic treatment, although no adverse effect was observed in the child[60]. In another case, a two week old infant whose serum levels were 25%

TABLE 5. Studies of exposure to lamotrigine during pregnancy

Author	*No. of pacients exposure*	*Diagnosis*	*Teratogenicity*
Rambeck, 1997	1	Epilepsy	No*
Tomson, 1997	1	Epilepsy	No****
Tennis, 2002	168	Epilepsy	No
Domínguez, 2001	40	Epilepsy	No
Cissoko, 2002	5	Epilepsy	One case: aplasia of the muscle of the lower lip and asimetrical abduction of the hip** One case: respiratory distress and apnea-bradycardia*** One case: respiratory distress and thrombocytopenia****
Ozkinay, 2003	1	Epilepsy	Dysmorphic traits**

*Multridrug therapy with valproic acid, weeks 0-3. **Multidrug therapy with valproic acid. ***Multidrug therapy with clobazam. ****Multidrug single drug therapy with lamotrigine.

of the maternal levels is described[62]. The third measures the serum levels of lamotrigine in three women and their children. The levels of the children went from 23% to 33% of the maternal concentrations[63]. Although none of the children experienced adverse effects, the concentrations reached levels that could generate side effects[44]. Thus, exposure of infants to lamotrigine presents a potential danger due to the increase in risk of severe rash in children with epilepsy who have been treated with this drug[20]. Clinicians should control the possible side effects, and if they are present, breast-feeding should be discontinued[43].

Oxcarbazepine

It is a 10-keto analogue of carbamazepine, whose pharmacokinetic profile is different from it, that decreases the interactions, with a more favorable profile, especially because of its limited involvement with oxidative microsomal enzymes[70]. It produces an increase in hormone metabolism and can increase the risk of contraceptive failures[71]. The studies performed in rats have not been able to demonstrate toxic effects in the mother nor have they altered the pre-embryonic development when this drug is administered during the first four days after fertilization[72]. In human beings (table 6), one case has been described of an epileptic patient who followed treatment with oxcarbazepine at a dose of 900 mg/day during pregnancy and also with carbamezepine during the first three months. At birth, the child presented the same concentrations as the mother, which suggests considerable placental passage. However, accumulation in the child was not detected in spite of the breastfeeding. Except for a mild facial dysmorphism, which has sometimes been observed due to carbamazepine, no neurological problems were observed at birth and there were no psychomotor problems; the child developed with normality when re-examined at 13 months of age[73]. Other studies that investigate fetal exposure to oxcarbazepine in vivo corroborate the findings of significant placental passage, as occurs with other anti-epileptic drugs[74]. Friis et al.[75] collected 12 cases of pregnancies in women who received oxcarbazepine in single or multiple therapy during the first quarter of the pregnancy. Three of the patients suffered abortions and the pregnancy was completed without problems in nine. There were no congenital malformations after exposure during the first quarter. Lindhout et al.[76] presented a series of eleven pregnancies prospectively controlled in which the pregnant women followed treatment with this drug. One case of spina bifida prenatally with multiple drug therapy was described, although no direct relationship was established between this malformation and oxcarbazepine. In a prospective study of 740 pregnancies in which the mothers had been exposed to old anti-epileptic drugs such as carbamazepine and valproic acid and new ones such as oxcarbazepine during the first quarter of pregnancy, it was found that the three drugs together with low folic acid concentrations increased the risk of malformations[77]. Although many authors recommend single drug therapy with the minimum doses possible in epileptic patients to control the seizure, this drug should only be used in pregnancy in bipolar patients, as occurs with the rest of the mood stabilizers, if the potential benefits justify the risk to the fetus.

Although it is known that oxcarbazepine is secreted in the maternal milk, no studies have been published beyond anecdotal cases on the use of oxcarbazepine during breast-feeding.

Other new mood stabilizers whose use in bipolar disorder is being studied, such as levetiracetam[78], vigabatrin[79] or zonisamide[44], have also not been analyzed sufficiently in regards to development of the fetus and its use in breast-feeding, so that prudent use is recommended until more information is available.

TABLE 6. Studies of exposure to oxcarbazepine during pregnancy

Author	*No. of pregnant women exposed*	*Diagnosis*	*Teratogenicity*
Bulau, 1988	1	Epilepsy	Mild facial dysmorphia*
Friis, 1993	12	Epilepsy	Three abortions, rest without malformations**
Lindhout, 2004	11	Epilepsy	One case of spina bifida***

* Multidrug therapy with carbamazepine. ** Single and multidrug therapy. *** Multidrug therapy with other anticonvulsants.

DISCUSSION

A drug is considered to be teratogenic when the prenatal exposure is associated with a significant increase in the risk of congenital physical anomalies over the baseline risk[80]. In general, all the psychodrugs available at present and their metabolites cross over the placenta, mainly by simple diffusion[81]. Lithium, valproic acid and carbamazepine are the traditionally used mood stabilizers in bipolar disorder. The three of them have demonstrated their teratogenic power[82]. Therapeutic management of the pregnant women with bipolar disorder poses several clinical dilemmas. Up to the moment, the absence of teratogenic potential of any of the mood stabilizers used up to now has not been demonstrated[83]. Furthermore, no specific malformation pattern has been described for any of these drugs[84]. Most of the articles reviewed coincide in stating that sufficient knowledge does not exist on the safety of the new mood stabilizers in pregnancy[85], although gabapentin and lamotrigine are mentioned as the least harmful for the fetus[86]. On the other hand, interruption, especially if it is sudden, of treatment with lithium and probably of the other stabilizers, is associated with a high risk of relapse that can

exceed the possibilities of relapse of the natural course of the disease without treatment[31,87] and can contribute to increasing the risk of suicide[88]. In a study published by Viguera[89], the recurrence rates after discontinuation of lithium were similar between subtypes I and II, but were greater in patients with a history of four or more previous episodes of disease and for those in whom the suppression had been faster. According to a recently published study in which women who sought advice prior to pregnancy in a medical center were evaluated, 45 % found that their psychiatrist advised them to avoid the pregnancy and 37% decided to do so. The reasons given most to make this decision were fear of teratogenic effects of the drugs and fear of the possibility that the disease would reoccur due to the discontinuation of the treatment[90].

As has been pointed out, most of them can cause failures in contraceptives so that higher doses of estrogens or additional methods are recommended.

The new anticonvulsants have also not been sufficiently studied in the case of breast-feeding to establish definitive recommendations. There have been opposite opinions, thus, on the one hand, we find the more conservative posture that consists in avoiding breast-feeding while these medications are used until more information is available[34] and, on the other, the tendency of other authors to consider that although the anticonvulsants are excreted in maternal milk, most of the mothers who require the use of these drugs can breastfeed safely without risks[91]. In this case, the maternal blood levels of the drug should be determined together with the clinical control of the child to evaluate his exposure to this substance. Descriptions of some sporadic cases suggest that maternal hepatic enzymatic induction of the anti-epileptic drugs increases the risk for neonatal breastfeeding. Thus the antenatal administration of vitamin K1 is insistently recommended for mothers who use these drugs. It is also recommended that all the women who aim to become pregnant continue treatment with folic acid prior to conception, especially if they are following treatment with anti-epileptic drugs[92].

No general guidelines on the use of the new mood stabilizers in pregnancy and breastfeeding are available after the analysis of the articles published about this subject, however it is important to consider that the treatment must always be adapted to the severity of the disorder of the patient, adopting individualized decisions. Treatment of bipolar disorder during pregnancy and post-partum, in a dynamic process, and the decisions on the therapeutic options may be modified over time, depending on the individual course of the disease in each patient. At present, it is advocated to analyze the risks derived from the interruption or maintenance of the treatment in detail, considering the risks that discontinuation of the mood stabilizer may have. Some authors[9] recommend performing a gradual discontinuation test of the stabilizer prior to the time of conception, in order to obtain information on the clinical condition of the patient without treatment, and the drug should be reintroduced with the first sign of relapse. Finally, it should be reevaluated if the pregnancy could be feasible without treatment. In other cases, it is recommended that medication with psychodrugs be suspended until the sixth week of pregnancy and that extensive monitoring be carried out during the final weeks in pregnant women with previous recurrences of type I typical bipolar disorder[10]. A multidisciplinary approach between the different specialists involved, based on information to the patient, is essential.

Thus, the teratogenic effects of some anti-epileptics should be considered and efforts should be made to define the risks better, especially with those of the new generation. It must always be taken into account that the combination of anti-convulsants increases the risk, probably due to the elevation of maternal plasma levels[93]. For future clinical decisions that are scientifically founded, the prospective data of the pregnancy records are essential to be able to characterize the possible teratogenic effects of the new mood stabilizers with greater accuracy. As conclusion, we can state that due to the lack of adequate and well controlled studies performed in bipolar women, both in the pregnancy as well as breast-feeding stage, all the new mood stabilizers in general should be used only in those cases in which the potential benefit justifies the risk on the fetus or infant.

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