Psychiatr. Pol. 2014; 48(5): 865–887
PL ISSN 0033-2674
www.psychiatriapolska.pl

Mood stabilisers and pregnancy outcomes: a review

Giulia Costoloni, Elisa Pierantozzi, Arianna Goracci,
Simone Bolognesi, Andrea Fagiolini

Division of Psychiatry, Department of Molecular Medicine,
University of Siena, School of Medicine
Head of the Department: prof. A. Fagiolini

Summary

The purpose of this review is to give useful information to guide clinicians when treating pregnant women affected by bipolar disorder. This review focuses on mood stabilizers including lithium, sodium valproate, carbamazepine, oxcarbazepine, gabapentin, lamotrigine and topiramate. Data have been extracted from a MEDLINE search. Data from prospective, retrospective and case-control studies as well as systematic reviews, meta-analysis and data from Pregnancy Registry were included. Major congenital malformations as well as specific malformations were reported for each drug. Preliminary findings seem to identify lamotrigine as one of the safest antiepileptic drugs to be used in pregnancy. Teratogenity risk of topiramate is still largely unknown and there are not enough studies to draw even preliminary conclusions. Preliminary studies failed to report an increased risk for major congenital malformations among gabapentin or oxcarbazepine exposed pregnancies. Even if raising less concern when compared to valproate, carbamazepine should be avoided for its documented teratogenity risk. Valproate seems to be the worst considering major congenital malformations, specific malformations as well as its detrimental effects on neurodevelopment. On the other hand, lithium might be considered a good option when treating pregnant women affected by bipolar disorder. Given the limited research on mood stabilizers in pregnancy, clinicians need to be very careful when treating child bearing age women. Clinicians have to balance the potential teratogenity risk against that of untreated mental illness considering individual circumstances such as severity of illness and risk of relapse.

Key words: pregnancy, mood stabilizers, teratogenity

Introduction

Not many studies have assessed the prevalence of bipolar disorder (BD) during pregnancy. A recent study reported a lifetime prevalence of 0%, 0,3% and 0,2% for bipolar I disorder, bipolar II disorder and BD NOS respectively. Unfortunately, this

study did not provide any information about pharmacotherapy [1]. Similar findings were found in a Swedish study: among 1,795 pregnant women, only one woman affected by BD has been reported. In this study 1 patient was taking antidepressant and 5.0% had received psychotherapy [2]. Another study assessed the prevalence of hypomania at 12 weeks of pregnancy reporting a prevalence of 1.4% [3]. A lower risk of having any mood disorder among pregnant women compared to non pregnant women was reported in a recent study [4]. These studies seem to show a low prevalence of BD during pregnancy. However, BD is a lifelong disorder and most women affected by it will require mood stabilizers throughout their pregnancy to prevent relapses. Mood-stabilizing drugs discontinuation has been related to a high risk for new morbidity, in particular for depressive and mixed episode. In a recent study the risk rate of new episodes of illness after lamotrigine discontinuation in pregnant women has been evaluated. In this study 100% of women experienced mood recurrence after the discontinuation while the recurrence risk rate was 30% among women who continued mood stabilizers treatment throughout their pregnancy [5]. Grof found the recurrence risk during pregnancy to be lower among pregnant women with bipolar I disorder than the one reported for childless women affected by the same mood disorder. All these women were not taking any psychotropic medication [6]. Bergink and colleagues stressed the importance of continuing treatment throughout all pregnancy and postpartum among women affected by BD. Among 41 women with BD, 24,4% experienced a mood episode during pregnancy, despite the use of lithium. Moreover, postpartum relapse risk was higher (60%) between women who presented relapses during pregnancy. On the contrary, the same authors did not suggest prophylactic treatment during pregnancy in women with history of postpartum psychosis. However, postpartum prophylactic treatment has been found to be effective among these patients, since no women (n=20) under treatment presented postpartum relapses while 44,4% of the women who refused treatment experienced postpartum psychosis [7].

Hence, it is necessary to evaluate the potential teratogenity of antiepileptic drugs (AED) commonly used for treating BD in order to understand whether or not teratogenity risk is bigger than those due to therapy discontinuation. When treating pregnant women clinicians have to balance potential teratogenity against the risks of uncontrolled maternal symptoms. Moreover, Boden and colleagues in a population based cohort study, found bipolar disorder to be associated with an increased risk of adverse pregnancy outcomes. This increased risk did not seem to be associated with mood stabiliser therapy since it has been reported among treated and untreated women. An increased risk of preterm birth (50%) was reported in both treated and untreated women affected by bipolar disorder. The risk rates of microcephaly among infants of treated and untreated women affected by bipolar disorder were 3,3% and 3,9% respectively. The risk rate among healthy women was 2,3%. Similar results were found for the risk

of neonatal hypoglycaemia: 3,4%, for treated women, 4,3% for untreated and 2,5% for controls. This study did not observe any statistically significant difference between treated and untreated women [8].

The purpose of this review is to provide useful information to guide the clinicians approaching pregnant women with BD. We focused on mood stabilizers including lithium, sodium valproate, carbamazepine, oxcarbazepine, gabapentin, lamotrigine and topiramate.

Methods

Data used for this review have been extracted from a MEDLINE search. Combination of the following keywords were used: bipolar disorder, pregnancy, teratogenity, antiepileptic drugs, mood stabilizers, major congenital malformation and neurodevelopment. The outcomes considered were perinatal teratogenity, major congenital malformation, specific malformations and neurodevelopment. Data from prospective, retrospective and case-control studies, as well as systematic reviews, meta-analysis and data from Pregnancy Registry evaluating pregnancy outcomes among women treated with mood stablisers were considered. We focused on data published between 2008 and 2013, although some older studies regarding specific malformations, not included in the reviews we considered, were reported. Some recent studies and case reports not included in the reviews have also been considered. All relevant paper published in English meeting the eligibility criteria were included. For each drug information about pharmacokinetic is given; for lithium, carbamazepine, valproic acid and lamotrigine perinatal teratogenity, structural teratogenity (major congenital malformation and specific malformation), and neurodevelopmental effects of prenatal exposure to antiepileptic drugs were reported. For drugs as topiramate, gabapentin and oxcarbazepine, such detailed information has not been reported, due to the lack of data. Moreover, the risk rate for monotherapy versus polytherapy has been evaluated whenever available in literature.

Lithium

Serum lithium concentration has to be monitored throughout all pregnancy in order to maintain lithium within the right range and to prevent potential toxicity. Pregnancy may increase creatinine clearance leading to a decline in serum lithium concentration to sub-therapeutic level. Moreover, the increased glomerular flow rate and plasma volume related to the third trimester might require an increased dose to maintain lithium within therapeutic range. On the contrary, a lower dose has to be used when the patient develops nausea and vomiting. An increased risk for serious toxicity is also represented by normal peri-partum diuresis and fluid volume loss.

Therefore it is necessary to check the blood level at least every 2- 4 weeks throughout all pregnancy, weekly from 36 weeks onwards and daily right before and right after the delivery. Moreover, lithium seems to equilibrate across placenta and poor perinatal outcome associated with high lithium concentration might be prevented or reduced by suspending it proximate to delivery. Intravenous hydration during labour and delivery should be considered when necessary and cord blood should be taken to exclude neonatal toxicity [9]. Stopping or reducing lithium prior to delivery, in order to prevent perinatal complications, has also been suggested by the Scottish Intercollegiate Guidelines (2012)[10].

Perinatal teratogenity

An increased rate of preterm birth, macrosomia [11], and perinatal mortality has been reported among lithium exposed pregnancies [12]. Moreover, an association between perinatal complications and plasma level of lithium at delivery have been reported in literature. Lithium exposure during pregnancy might lead to several neonatal complications including lower Apgar score as well as neuromuscolar and central nervous system complications. Regarding neuromuscular complications iporeflexia, lack of muscle tone and flaccidity have been reported by Dodd and colleagues, even when lithium was within therapeutic range. These symptoms characterize the “Floppy baby syndrome”, a very serious condition that might lead to death due to hypotonia, respiratory distress, lethargy, asphyxiation. The same authors found cardiovascular toxicity including cardiomegaly, supraventricular tachycardia, bradycardia, atrioventricular block [12]. A recent review confirmed what was previously reported, showing an association between lithium exposure and an increased risk for birth complications including preterm birth, hypotonia and respiratory distress [13]. Renal disfunction such as nephrogenic diabetes insipidus and thyroid toxicity have also been reported [11]. In a prospective multicentre study Jacobson and colleagues found that lithium exposed infants weighed a mean of 92 g more than controls at birth ($p=0.01$), while gestational age did not differ between the groups ($p=0.56$)[14].

Major congenital malformations

In a prospective multicentre study, Jacobson and colleagues evaluated the pregnancy outcome among 138 lithium exposed pregnancies. This study failed to report an increased major congenital malformation (MCM) rate among exposed pregnancies (2,8%) compared to controls (2.4%). One Ebstein’s anomaly was reported among lithium exposed group [14]. A recent review didn’t report any significant increased risk for MCMs associated with lithium exposure [15]. Similar findings were reported

by McKnight and colleagues in a recent meta-analysis including 385 studies. The authors did not report a significant increased risk of congenital malformations[16]. Even though there are some concerns regarding specific risk for Ebstein's anomaly, lithium has been identified by Gentile as the first choice drug to be used in pregnancy [17].

Specific malformations

An association between lithium exposure and an increased relative risk of Ebstein's anomaly has been reported in the past several times. However, Cohen and colleagues found the relative risk for Ebstein's anomaly among first trimester lithium exposed pregnancies to be consistently lower than previously reported. The authors evaluated four case-control studies involving 25, 34, 59 and 89 Ebstein's anomaly affected children finding no history of lithium exposure [18]. Similar findings were reported in two recent reviews [11],[13]. On the other hand, a recent review confirmed the association between lithium exposure during pregnancy and cardiac defect Ebstein's anomaly [17].

Neurodevelopment

In an observational retrospective cohort study the effect of lithium on growth, cognitive, neurological and behavioral development at 3-15 years of age was assessed among lithium exposed pregnancies. This study didn't show any detrimental effects of lithium on neurodevelopment [19].

Carbamazepine

After oral intake, carbamazepine (CBZ) is erratically absorbed and the binding to plasma proteins is about 70%. CBZ is metabolized in the liver by CYP3A4 and its metabolite 10,11 epoxide is also active. By inducing other subtypes of CYP450 and UDP-glucuronosyl transferase this AED enhances the metabolism of other compounds. During pregnancy serum concentration of CBZ can decrease by 25%. While in the first trimester these changes are not relevant, at the later stages total plasma concentration and free plasma concentration have been shown to decrease [20].

Perinatal teratogenity

A recent case report described the "fetal carbamazepine syndrome", characterized by facial dysmorphism, cardiovascular, nervous system, urinary tract and skeletal anomalies. Four pregnancies of a patient on CBZ were analyzed, and all of them

reported anomalies. The authors reported on the actual pregnancy, which lead to a female showing facial dysmorphism, hypoplasic nails, xyphosis and myelomeningocele. The infant died at seven days due to multiple organ failure [21]. Severe consequences of CBZ exposure in utero were also reported by Akar and colleagues. A case of fetal CBZ syndrome characterized by facial dysmorphism, heart defect, skeletal abnormalities, renal agenesis, ambiguous genitalia, anal atresia and right hemihypoplasia of the entire body was described [22].

Major congenital malformations

A recent review evaluated the teratogenity risk of MCMs among CBZ exposed pregnancies. All the meta-analysis and studies included in this review will be reported in what follows. A meta-analysis showed an association between CBZ exposure in utero and a higher risk of MCMs (5.5%). Similar findings were reported in a systematic review and meta-analysis. From the analysis of 4411 CBZ exposed pregnancies, a MCM rate of 4,6% was reported. However, the teratogenic potential of CBZ was significantly lower when compared with other AED. A recent review also failed to find a statistically significant increased risk of malformation among CBZ exposed infants. Morrow and colleagues examined 900 CBZ exposed pregnancies finding only 20 MCMs (2,2%) (odds ratio 1.0) [23]. Similar results were reported by Jentink and colleagues who found an overall prevalence for a MCMs of 3,3% due to CBZ monotherapy during the first trimester. Moreover, they found spina bifida to be the only specific malformation due to CBZ. There was no clear evidence of an association between CBZ exposure and anomalous pulmonary venous return, cleft lip, diaphragmatic hernia or hypospadias [24]. From the observation of the United Kingdom Epilepsy and Pregnancy Register Campbell and colleagues failed to find a higher risk for recurrent malformations in pregnancies exposed to CBZ [25]. The risk of major malformations among infants exposed to antiepileptic drug monotherapy during the first trimester and among an unexposed group was also calculated by Hernandez and colleagues. The risk rates for valproate, topiramate, carbamazepine and lamotrigine were 9,3%, 4,2%, 3,0% and 2,0% respectively [26]. Amongst monotherapies, MCM prevalence was highest with valproate (11.3%; p=0.005) while lamotrigine (5.4%; p=0.23) and CBZ (3.0%; p=0.65) were closer to controls (2.1%). Vajda and colleagues analysed data collected by the Australian Pregnancy Register. No MCM were associated with CBZ monotherapy exposure [27]. Another study by the same authors found a malformation rate of 5,0% for CBZ monotherapy. The malformation rate was considerably lower than the one observed with valproate (14,5%), but slightly higher than what was observed among unexposed pregnancies (3,15%) [28]. Holmes and colleagues evaluated the risks of malformation comparing polytherapy and monotherapy groups, finding a 2.9%

risk rate among CBZ monotherapy exposed pregnancies. The risk was higher for infants exposed to CBZ as polytherapy (15,4% for CBZ plus valproate and 2,5% for CBZ plus any other AEDs) [29].

Specific malformations

An association between orofacial clefts and CBZ exposure has been observed in the past. CBZ exposure has also been associated with an increased risk of neural tube defects [24][30]. Recently, an association between CBZ exposure in utero and renal tract abnormalities has been reported [31]. A significant reduction of mean head circumference was observed among infants exposed to CBZ during pregnancy ($p<0.001$) [32]. An increased risk for being born small for gestational age has been observed in CBZ exposed pregnancies [33].

Neurodevelopment

Findings regarding the effects of CBZ on neurodevelopment are still controversial. A 2010 meta-analysis of 7 studies analysed full scale, verbal and performal IQ scores in 151 CBZ exposed children and in 494 unexposed controls. Among the control group there were children born to healthy women or to women with untreated epilepsy. The full scale IQ and Verbal IQ found among CBZ exposed children were not statistically different from those of the control group ($p=0.095$ and $p=0.097$) while Performal IQ was statistically significant lower in the exposed children compared to controls ($p<0.02$). The mean VIQ, PIQ and FSIQof the exposed children was not statisticallydiffernt from the control-epilepsy group ($p=0.39$,$p=0.19$ and $p=0.41$) [34] Recent studies have suggested that CBZ exposure does not seem to decrease average reported IQ, cognitive fluency and originality and language skills [35]. On the contrary, a recent study found a correlation between in utero exposure to CBZ and a significant detrimental effect on neurodevelopment ($p<0.01$) [36].

Valproic acid

Valproic acid (VPA) is largely used as an anticonvulsivant drug as well as a mood stabiliser for treating BD. After oral administration, it is absorbed in the gastrointestinal tract and about 90% is bound to plasma proteins. A small quantity of VPA is excreted unchanged. In pregnant women, total plasma concentration of VPA can decrease from 25% to 50%. However, the active unbound drug seems to maintain a stable level throughout pregnancy [20]. An increased risk of MCMs has been reported for higher doses [26].

Perinatal teratogenity

VPA exposure in utero has been associated with a foetal valproate syndrome characterized by cardiac, facial and central nervous system anomalies and intrauterine growth restriction [37]. Ozkan reported the case of an infant with multicystic dysplastic kidney, complex cardiac defect, trigonocephaly, limb and facial defect due to low dose VPA monotherapy exposure in utero (250 mg/day) [38].

Major congenital malformations

A few meta-analysis and studies included in a a recent review by Wlodarczyk and colleagues will be reported in what follows. A 2008 meta-analysis reported a 10,7% risk rate of MCMs among 2097 infants exposed to VPA monotherapy during pregnancy. These findings seem to confirm what was previously reported in two different retrospective studies who found a risk rate for MCMs after VPA monotherapy exposure of 9,7% and 10,7% respectively. A similar risk rate (11,1%) was also recently found in a controlled observational study [23]. Similar findings were reported by the analysis of the North American AED Pregnancy Registry. The incidence of malformations was assessed among infants exposed to different AED in monotherapy during the first trimester and among a control group. A MCM risk rate of 9,3% was reported for VPA, considerably higher than what was found for any other AED. The risk of MCM was 4,2% for topiramate, 3,0% for CBZ, 2,0% for lamotrigine. Compared with lamotrigine, the RR was 5.1 (95% CI 3.0-8.5) for valproate and 2.2 (95% CI 1.2-4.0) for topiramate [26]. Tomson analysed data from almost 5000 monotherapy exposures. The incidence of MCMs was reported to be 9,7% for VPA, 2,9% for lamotrigine and 5,6% for CBZ. The lowest risk rate was found for lamotrigine monotherapy at doses lower than 300 mg per day while MCMs risk rate was higher for VPA at all investigated doses [39]. A higher risk was reported by Vajda and colleagues in two different studies which reported MCMs risk rate of 16,8% and 13,3%, respectively [23]. From the observation of the Australian Pregnancy registry Vajda found an increased risk for MCMs among VPA monotherapy exposed pregnancies (MCM by 1 year 15,2%; odds ratio: by 1 year versus no AED 4,99; 95%CI 1,73, 14,44 $p<0.05$) compared to lamotrigine (4,9%; OR 1,48; 95% CI 0,47, 4,69) and CBZ (5,3%; OR 1,59; 95%CI 0,52,4,97) monotherapy exposure. The risk rate was 3,4% among controls [40]. Recently, Vajda and colleagues, evaluated the teratogenity risk among women exposed to VPA, lamotrigine or topiramate in monotherapy during first trimester. The incidence of malformations was considerably higher for valproate (16,3%) when compared with lamotrigine (5,2%), topiramate (3,2%) and no exposure (5,2%). Moreover, the VPA-associated malformations rate was dose related ($p<0.0001$) [27]. These data suggest that VPA is a significant teratogen, a fact that was recently confirmed in another study [28]. A MCM risk rate

of 14,5% among valproate exposed pregnancies was reported, significantly higher than reported for no AED exposure (14,5% versus 3,15%; OR=5.23; 95% confidence interval=1.81; 15.09)[28].From the analysis of the United Kingdom Epilepsy and Pregnancy Register, Campbell reported the incidence of malformations among VPA exposed pregnancies to even higher than previously found (21.9%, relative risk 1.47, 95% confidence interval [CI] 0.68-3.20). However, this study reported a MCM risk rate of 9,8% (relative risk 1.73, 95% CI 1.01-2.96) among controls, which is also considerably higher when compared to what observed in other studies. The incidence of malformations was 16,8% for women who already had a child with MCMs. This study also suggests that genetic influences may play a role determining the teratogenic risk of antiepileptic drugs [25]. On the contrary, a considerably lower risk rate was reported by Samrén (5,7%) and by Morrow (6,2%) [23].

Specific malformations

Associations between valproate exposure and specific congenital malformations has also been evaluated. An increased risk of neural tube defects has been repeatedly reported after VPA exposure [24, 26, 31]. Drug-specific increased risk was observed for VPA in relation to oral clefts and hypospadias [24]. On the contrary, a recent study by Vajda [31] failed to observe an association between hypospadias or cleft palate/lip and VPA exposure. An increased risk for either congenital jaw or oral malformations was recently reported by Koo and Zavras [41]. Heart defects [24, 26, 31], polydactyly, skull bones and brain abnormalities after in utero exposure to VPA were also reported [24, 31]. A recent study by Pennel [33] reported increased risks of being born small for gestational age and transiently reduced Apgar scores among infants exposed to VPA during pregnancy. A significative reduction of mean head circumference has been reported after VPA monotherapy exposure (p=0.04) [32].

Neurodevelopment

Meador [42] evaluated the neurodevelopmental effects of VPA exposure in utero, suggesting VPA exposure is a risk factor for cognitive impairment in children. Children exposed to VPA during pregnancy showed the poorest cognitive results at 3 years of age, compared to the IQs of their mothers, while a correlation between maternal and offspring's IQs was observed for CBZ and lamotrigine. An association between poor long-term child developmental outcomes and VPA exposure has been recently reported, confirming what previously suggested [36]. A reduced level of intelligence among children exposed to VPA during pregnancy was also reported in a recent meta-analysis by Banach and colleagues who showed mean full-scale IQ (FSIQ), Verbal IQ (VIQ) and performance IQ (PIQ) to be significantly lower in the

VPA group compared with the unexposed group (p=0.001, p=0.001 and p=0.007). The mean FSIQ, VIQ and PIQ scores in VPA in utero exposed children were 83.9 (95% CI 64.2, 103.6), 93.7 (95% CI 72.6, 114.7) and 88.3 (95% CI 69.9, 106.9), respectively. The mean FSIQ, VIQ and PIQ scores in the control group were 102 (95% CI 90, 116), 101 (95% CI 87, 114) and 99 (95% CI 90, 117), respectively [34]. Recent studies have shown a correlation between VPA exposure during pregnancy and cognitive fluency and originality impairment. Moreover, VPA exposure in utero seems to be linked with impaired verbal acquisition, maladaptive behavior and reduced language skills [35]. An association between fetal VPA exposure and poor cognitive outcome has also been reported by Meador. Moreover, a negative correlation was reported between high doses of VPA and IQ, verbal and non-verbal ability, memory and executive function [43]. A recent observational study found an increased risk of early cognitive development delay among VPA exposed children compared to children exposed to Levetiracetam ($p < 0.001$). Children exposed to LEV did not differ from control children ($p = 0.62$) on overall development. The study did not compare VPA exposed pregnancies and control group [44]. However, a decreased verbal versus non verbal abilities at three years of age was observed for each drugs, suggesting a correlation between in utero exposure to all AED and detrimental effect on neurodevelopment [45]. Moreover, a population based study found an association between valproate exposed pregnancies and an increased risk of both childhood autism and autism spectrum disorder. In particular, an absolute risk of 4,42% was reported for autism spectrum disorder among children exposed to valproate during pregnancy. Among the same sample, a risk of 2,50% for childhood autism was found. The absolute risk for autism spectrum disorder and autism among unexposed children was 2,44% and 1,02%, respectively [46].

Monotherapy and polytherapy

Polytherapy including VPA seems to be associated with a higher risk of MCMs than combinations not containing VPA. Cunnington and colleagues [47] reported the risk rate for MCMs to be 12,5% after lamotrigine plus VPA polytherapy. The risk rate was considerably lower for lamotrigine plus any other anti epilectic drugs (2,7%). A recent study reported the risk rate of MCMs following lamotrigine plus VPA polytherapy exposure to be similar to the risk rate found for VPA monotherapy [48]. Similar findings were reported by Holmes [29] from the observation of MCMs among infants exposed to lamotrigine as polytherapy. The risk rate was 9,1% for lamotrigine plus VPA and 2,9% for lamotrigine polytherapy without VPA. For CBZ the risk rate for VPA polytherapy and any other AEDs were 15,4% and 2,5%, respectively. These results seem to suggest an increased risk rate of MCMs for lamotrigine and CBZ as polytherapy compared to monotherapy, only when VPA is included. However, Vajda found the risk

rate for MCMs among infants exposed to VPA to be higher in monotherapy (17,9%) than in polytherapy (7,26%). Therefore, more studies are needed to clarify whether or not is VPA polytherapy associated with a higher risk rate of teratogenity compared to monotherapy [49].

Lamotrigine

Lamotrigine is a wide spectrum antiepileptic drug (AED) and it is also used as a mood stabilizer for mood disorders. During pregnancy there is a significant increase of the enzymatic induction of the N-2 glucuronide pathway. As a result the plasma concentration of this AED can decrease by more than 50%, and increases in doses up to 50% might be necessary. Clearance of lamotrigine increases gradually up to 32nd week and during the last month it can reach a level three times higher than before pregnancy [20]. Right after partum lamotrigine elimination suddenly decreases; during the two first weeks after delivery one can observe a peak in serum concentrations. After 2-3 weeks there is the return to the levels observed before pregnancy.

Major congenital malformations

Many studies have suggested that lamotrigine is safer than other commonly used AED [12]. The limited existing data suggest lamotrigine to be less teratogenic than valproate [25]. Morrow and colleagues analyzed the effect of lamotrigine monotherapy in 647 exposed pregnancies finding that prenatal exposure to this drug caused fewer MCMs (MCMs) than valproate monotherapy. The rate of lamotrigine-induced MCMs was 3,2% with an OR of 1.44 (95% CI 0.77-2.67) versus 3,5% of the unexposed group. The MCMs rate for valproate exposures was 6,2% with an OR of 2.78 (95% CI 1.62-4.76) considerably higher than lamotrigine exposed pregnancy. Morrow also found an increased risk of MCMs (5,4%) when lamotrigine was given at daily doses higher than 200 mg [23]. On the contrary, both more recent studies and the observation of the Pregnancy Registry failed to observe an increased MCMs frequency with increasing lamotrigine dose [49][47]. From the observation of North American AED Pregnancy Registry Hernandez and colleagues [26] found that the risk of major malformations was considerably lower for lamotrigine (2,0%) than for any other AED. The risks of MCM for valproate, carbamazepine and topiramate were, respectively, 9,3%, 3,0% and 4,2%. The sample of the study was composed of pregnant women exposed to specific AED in monotherapy during the first trimester. Vajda reached a similar conclusion by observing the incidence of teratogenity among infants exposed to AED in monotherapy during pregnancy. The incidence of teratogenity was 4,9% for lamotrigine (OR 1,48; 95% CI 0,47, 4,69), 5,3% for carbamazepine (OR 1,59; 95%CI 0,52,4,97) and 15,2% for valproate (OR

4,99; 95%CI 1,73, 14,44 p<0.05) [40]. From the observation of the Australian Pregnancy Registry Holmes found the risk of malformation among infants exposed to lamotrigine as monotherapy to be even lower (1,9%), confirming lamotrigine to be one of the safest AED to be used in pregnancy [29]. Similar results were found by Tomson from an observational cohort study whose sample was composed of pregnant women exposed to AED in monotherapy. The lowest rates of malformation was seen for lamotrigine at daily doses below 300 mg (2,0%). A higher risk was found for valproate (at all investigated doses) and for carbamazepine (3,4% at doses less than 400 mg per day)[39]. From a controlled observational study Mawer found that amongst monotherapies MCM prevalence was highest with valproate (11.3%; p=0.005) while lamotrigine (5.4%; p=0.23) and carbamazepine (3.0%; p=0.65) were slightly above the controls (2.1%) [23]. These findings are different from what was reported by previous studies who did not observe an increased risk of pregnancy complicated with major birth defects in lamotrigine exposed pregnancy compared to unexposed one [25]. Vajda [27] by analysing data from The Australian Pregnancy Register found the rate of malformation among infants exposed to lamotrigine montherapy to be the same of the one observed among children of untreated women (5,2%). The same study reported a risk rate of 3,2% for topiramate, 16,3% for valproate and 6,3% for carbamazepine. Logistic regression analysis did not show statistically significant trend for the risk of MCM to increase with dosage p= 0.595).Similar findings were reported more recently by Campbell [25] from the analysis of the UK Epilepsy and Pregnancy Registry who observed an increased risk for malformation in pregnancy exposed to valproate (21.9%, relative risk 1.47, 95% CI 0.68-3.20) and topiramate (50%, relative risk 4.50, 95% CI 0.97-20.82), but no increase for carbamazepine and lamotrigine. From a population-based cohort study, Mølgaard-Nielsen reached the same conclusion. Among infants exposed to lamotrigine during the first trimester, the MCM risk rate was reported to be 3,7%, suggesting no association between lamotrigine exposure and major birth defect [50].

Specific malformations, neurodevelopment and perinatal teratogenity.

Although Pregnancy Registries have consistently shown lamotrigine to be one of the safer medications to be administered during pregnancy, considering both fetal malformations and postpartum cognitive development [23] [36], recent research suggests that exposure to lamotrigine could increase the risk of orofacial clefts in the offspring of lamotrigine exposed women [41]. The risk of cleft lip and/or palate among infants exposed to lamotrigine during pregnancy has seen to be 0,4 % higher when compared to other mood stabilisers. On the contrary Hunt analyzed the effect of lamotrigine monotherapy in 1,151 exposed pregnancies finding only a single case of isolated cleft palate [23]. Lamotrigine monotherapy doesn't seem to increase the rate

of microcephaly [32]. Recent studies failed to observe reduced Apgar Scores and SGA (small for gestational age) among infants exposed to lamotrigine, confirming this AED to be among the safest to be used in pregnancy [32, 33].

Topiramate

The increased renal blood flow in pregnancy leads to increased renal clearance of topiramate, therefore serum concentrations of topiramate have been seen to be reduced by 30-40% during pregnancy. Only 20-30% is metabolized while the remainder is excreted unchanged by the kidneys and can be found in urine [23].

Major congenital malformations, specific malformations and neurodevelopment

The safety of topiramate in pregnancy is largely unknown and there are few studies regarding the association between the risk of MCM and topiramate exposure in utero [23].Hunt found an increased risk for MCM among infants exposed to topiramate in utero; the risk seemed to be higher mainly for oral cleft and hypospadia [23]. These data seem to be similar to what was observed more recently; in fact a correlation between topiramate exposure and hypospadias was found by Vajda [31] while an increased risk of congenital jaw and oral malformation was observed by Koo and Zavras [41]. An association between first-trimester topiramate monotherapy and cleft lip/palate was also reported recently by Hernandez [26]. A recent study by Hernandez found the risk rate for major malformations among first trimester exposed pregnancies to be 4,2%. The risk rate for valproate, carbamazepine and lamotrigine were 9,3%, 3,0% and 2,0% respectively. Moreover, this study reported an association between topiramate exposure and cleft lip (1,4%) [26]. On the contrary, a recent retrospective study suggested little or no increase in risk of oral cleft or MCM compared to other antiepileptic drugs [51]. An increased risk for malformations among infants exposed to topiramate in utero was also reported by Campbell (50%, relative risk 4.50, 95% CI 0.97-20.82) [25]. The risk rate for topiramate was significantly higher than the risk observed in pregnancies exposed to valproate. This study didn't report an increased risk for malformations in lamotrigine and carbamazepine exposed pregnancies. From the analysis of the Australian Pregnancy Registry the incidence of malformations associated with topiramate monotherapy in the first trimester was reported to be 3,2%, even lower than the risk found for untreated women (5,2%). The risk rates for valproate and carbamazepine were 16,3% and 6,3% respectively. Logistic regression for the relationship between MCM risk rate and dose did not show any statistically significant trend of MCM to increase with dosage (p= 0.768) [27]. A population-based cohort study reported a risk rate for major birth defect to be 4,4%. This risk was assessed among infants exposed to topiramate during first trimester [50]. Ornoy

reported an association between topiramate exposed pregnancies and decreased birth weight. However, this study failed to observe an increased risk for structural defect [23]. Finally, Uludag reported multiple fetal anomalies in the children of women who were exposed to topiramate (200mg) and oxcarbazepine (300 mg) during pregnancy [52]. Few studies have focused on development of children exposed to topiramate in utero. Preliminary findings suggest that topiramate exposure may have an effect on the development of children; a group of nine children exposed in utero to topiramate monotherapy performed significantly worse than the control group (18 children)in a range of areas including visual and motor function as well cognition and behavior. Statistically significant diferences between groups were reported for general IQ (p=0.005), non verbal IQ (p=0.011) verbal IQ (p=0.017) [53].

Gabapentin

Gabapentin is almost completely absorbed after oral intake and it can be found as unchanged metabolite in urine. During pregnancy its serum concentration can decrease(considerably due to the increased renal blood flow [23].

Major congenital malformations and specific malformations

Morrow reported one MCM, a ventricular septal defect, among 31 women treated with gabapentin monotherapy during pregnancy. The risk rate was 3,2 % which was not statistically significant (p= 0,782) [23]. More recently a population based cohort study reported no correlation between first trimester gabapentin exposure and major birth defects (risk rate 1,7%) [5]. On the contrary, Koo and Zavras reported an increased risk of congenital jaw and oral malformation in gabapentin exposed pregnancies [41]. A recent prospective study by Fujii compared the outcomes of 223 gabapentin exposed pregnancies with 223 unexposed pregnancies, finding no increased risk of malformations among exposed infants (p = 0.845) [54]. However, a higher risk rate of preterm birth (p = 0.019) and low birth weight <2,500 g (p = 0.033) were reported in the exposed group. Finally, the findings in pregnancy cohort and case-control studies have been analysed by Holmes and Hernandez who showed no evidence of teratogenity [55]. Gabapentin monotherapy doesn't seem to increase the rate of microcephaly [41]. Even if preliminary findings failed to observe an increased risk of MCM related to gabapentin exposure, more data from monotherapy trials are needed to clarify potential teratogenity of gabapentin.

Oxcarbazepine

After oral administration, oxcarbazepine is quickly metabolized to monohydroxycarbazepine, whose protein binding is about 40%. The pharmacologically active monohydroxycarbazepine is then eliminated as a glucuronide. During pregnancy, serum concentration of this active metabolite are at least 36% lower than compared with pre and post-pregnancy values. The decreased serum concentration seems to be a consequence of both the increased rate of glucuronidation and the increased renal excretion observed during pregnancy. A few weeks after delivery there is a return to pre-pregnancy levels. Pertreinate through the analysis of 13 women who were treated with oxcarbazepine monotherapy during pregnancy reported a significant decrease of ratio plasma concentration of 10-monohydroxy (MHD) of oxcarbazepine. The serum concentration was seen to be reduced by 26,2% during first trimester, by 36,5% during second trimester and by 38,2% during third trimester [56].

Major congenital malformations and specific malformations

From a population based cohort study Artama and colleagues didn't report an increased risk for malformations in offspring of mothers using oxcarbazepine as monotherapy or polytherapy without valproate [30]. Two hundred and forty eight pregnancies exposed to oxcarbazepine monotherapy and 61 expose to polytherapy were analyzed in a review by Montouris. Six malformations were reported among infants exposed to oxcarbazepine monotherapy (2,4%). The risk rate observed in the general population was 2-4%. A higher risk rate (6,6%) was found among infants exposed to polytherapy including oxcarbazepine [57]. More recently, Moolgard-Nielsen and Hviid, seemed to confirm what previously observed by Montouris. From a population based cohort study a risk rate for MCM of 2,8% was reported among infants exposed to oxcarbazepine monotherapy during the first trimester [50]. The effect of polytherapy involving oxcarbazepine has also been evaluated. Uludag and colleagues reported a case of a woman treated with topiramate (100 mg) and oxcarbazepine (300 mg) during pregnancy. MCMs including limp defects, cardiomegaly, orofacial cleft, absent right kidney were found by ultrasound and confirmed by autopsy after induced labor. However, the malformation rate for oxcarbazepine monotherapy was calculated to be 2,4%, similar to the risk rate observed in the general population [52]. Considering polytherapy including phenobarbital, only one cardiac malformation was reported in a study involving 55 pregnancies [12]. Even if preliminary findings failed to observe an association between fetal exposure to oxcarbazepine and the risk of major birth defects, the number of studies involving maternal exposure to oxcarbazepine is not sufficient to draw a definitive conclusion.

Conclusion

BD is a lifelong relapsing and remitting disorder. Maintenance treatment as well as support are needed to prevent relapses, improve quality of life and functioning. Hence, most of women affected by BDs will require drug treatment throughout their pregnancy to prevent relapses. As previously reported, a higher rate of new morbidity has been associated with mood stabilizing drugs discontinuation during pregnancy [58]. On the other hand, there are no specific drugs licensed for being used during pregnancy. Moreover, according to the guidelines, drugs such as valproate, carbamazepine, lithium and lamotrigine should not be used for their documented teratogenity risk. The teratogenity risk associated with lithium seems to be lower than reported in the past and specific guidelines are given to monitor serum lithium levels during pregnancy. Antipsychotic are considered a safer option when compared to mood stabilizers when treating patients during pregnancy [59]. To sum up, the risk of teratogenity associated with psychotropic medication has to be balanced with the risk of uncontrolled maternal symptoms. Moreover, when treating pregnant women with BD, clinicians have to consider potential teratogenity risk in the context of individual circumstances. Several elements such as age, genetic profile, comorbidity, severity and duration of illness, tolerance and pharmacokinetic profiles need to be considered when choosing a mood stabilizer for each patient. Pregnancy represents a peculiar situation leading to change in drug concentration and pharmacokinetics. Potential drug interactions also have to be considered. For each drug the safe dose that will treat the disease without potential teratogenic effects remains to be determined. Hence, the lowest efficacious dose is recommended to minimize the potential teratogenic risk. More human studies are needed to clarify potential teratogenity risk for each drug. Moreover, in order to draw definitive conclusion larger numbers of studies evaluating monotherapy exposure are needed. There is also not an adequate follow up of children in later developmental periods since most of the studies have focused only on structural teratogenity. Preliminary findings seem to identify lamotrigine as one of the safest AED to be used in pregnancy. Considering its protective effect in prevention of bipolar disorder and its reproductive safety profile LMT has been identified as one of the safest mood stabilisers for treating BD during pregnancy by the American College of Obstetricians and gynecologist (ACOG) [60].Similar findings were reported in the Scottish Intercollegiate Guidelines. However, the risk of postpartum maternal toxicity has to be considered and maternal lamotrigine levels should be monitored after delivery [10]. Teratogenity risk of topiramate is still largely unknown and there are not enough studies to draw even preliminary conclusions considering both structural teratogenity and neurodevelopmental effects. Even if experience with gabapentin use in pregnancy is very limited, preliminary studies failed to report an increased risk for MCM among infants exposed to gabapentin during pregnancy. Preliminary studies did not report an association between in utero oxcar-

bazepine exposure and the risk of major birth defects. Even if raising less concern when compared to valproate, carbamazepine should be avoided for its documented teratogenity risk. Avoiding cabamazepine and valproate, especially during the first trimester, has been suggested by the practice bulletin of ACOG [60]. Also according to the Scottish Guidelines (2012) valproate should be avoided when treating women in their fertile age. If alternatives are not available or indicated, contraceptive measures should be suggested. Moreover, all women taking AED should take daily dose of 5 mg of folic acid from preconception up to the end of the first trimester[10].While valproate seems to be the worst considering MCMs, specific malformations as well as its detrimental effects on neurodevelopment, lithium might be considered a good option when treating pregnant women affected by BD. Potential neonatal toxicity might be prevent by suspending lithium proximate to delivery. The practice bulletin developed by The American College of Obstetricians and Gynecologist (ACOG) gave useful information for management of women affected by BD who are planning to conceive. Regular foetal assessment with echocardiography should be recommended for all pregnant women taking lithium. In women who experienced severe and frequent mood episodes, lithium should be continued throughout the pregnancy. In women who reported moderate episodes, lithium should be tapered before conception and re-introduced after the first trimester. In women at low risk for relapses lithium should be tapered before conception [60].

The Scottish Intercollegiate Guidelines (2012) stressed the importance of starting prophylactic medication right after delivery in order to prevent relapses [10]. Finally, considering that many pregnancies are unplanned, clinicians need to be very careful whenever treating women in their fertile years. Whether or not they're planning a pregnancy, all women of child-bearing potential, need to be informed about risks associated with pregnancy; the risks include both drugs related teratogenity potential as well as the risks of relapses when changing or stopping treatment. According to what was previously reported, the avoidance of polytherapy is a good principle when treating women of child bearing age. Moreover, The World Federation of Societies of Biological Treatment of Bipolar Guidelines (WFSBP) suggested prescribing monotherapy and switching treatments when ineffective, whenever treating people affected by BD [61]**.** While pregnant women have to be informed about the potential teratogenity risks associated with any prescribed drug versus the risk of untreated disorder, non-pregnant women have to be informed about all the potential side effects including teratogenity, of any prescribed drugs. One feature that is shared by the literature on the several AED reviewed here is the clear need for more studies in order to clarify their potential teratogenity risk. It is not the purpose of this review to give guidelines about BD in pregnancy but to give fully complete information about the potential teratogenity risk of mood stabilisers. For this reason, other drugs recommended from the guidelines for BD, including antipsychotics that act as mood

stabilisers, have not been evaluated. For completeness sake, some information about treatment of BD will be provided. Goodwin reviewed the first BAP (British Association for Psychopharmacology) providing evidence-based guidelines for treating BD. Concerning pregnancy, he reported a higher teratogenic risk associated with antiepileptic drugs including lithium ,while a lower risk was associated with antipsychotics. Moreover, different phases of BD require different treatments. For severe manic episode antipsychotic or valproate are suggested as first line treatment. Lithium should be consider as an alternative to antipsychotic or valproate for mild manic episode. For mild or moderate depressive episodes quetiapine or lamotrigine are considered first choice drugs. If mania predominates lithium and valproate are suggested as first line treatment; a good alternative might be aripiprazole, quetiapine or olanzapine. As a second line treatment carbamazepine should be considered. Lamotrigine and quetiapine are reported as first line treatments when depression predominates, with lithium as a second line treatment. Guidelines also stressed the importance of considering maintenance therapy after recovering from an acute episode, especially for Bipolar I disorder[62].The clear need of prophylactic treatment has been underlined by the World Federation of Societies of Biological Psychiatry (WFSBP) in its 2012 update. According to WFSBP guidelines, both carbamazepine and lithium raise major concerns regarding safety and tolerability (ST). In terms of practicabilty (PR) some aspects make their use difficult in clinical practice. The same concern about PR has been reported for gabapentin. Considering ST gabapentin, lamotrigine and topiramate has been identified as good options. Both advantages and disadvantages are reported for LMT considering PR. Topiramate and valproate give the possibility of choosing between different formulations and are unlikely to give discontinuation effects in terms of PR. Equally advantages and disadvantages have been reported for oxcarbazepine in terms of PR and for oxcarbazepine and valproate in terms of ST. Regarding the effects on suicide prevention, conflicting data are reported for carbamazepine, gabapentin, lamotrigine, oxcarbazepine and valproate. Good evidence regarding the prevention of suicide has been associated with lithium therapy, while topiramate may enhance suicidal ideation. Recommendation grade 1 for long-term treatment has been established for lamotrigine and lithium, based on category of evidence (CE) A from controlled studies and good risk-benefit ratio. The recommendation grade for valproate is 3 based on CE B (limited positive evidence from controlled studies). Carbamazepine, gabapentin, oxcarbazepine and topiramate has been associated with recommendation grade 4 considering CE C (evidence from uncontrolled studies or case report/expert opinion) [61]**.** A third update (2013) of the original 2005 guidelines for the management of bipolar disorder has been recently published by the Canadian Network for Mood and Anxiety Treatments (CANMAT). For manic episode, lithium, valproate and atypical antipsychotic are considered to be first-line treatments. Asenapine, paliperidone and sodium valproate can also be used

as first-choice drugs for mania. Lithium, lamotrigine and quetiapine monotherapy are considered first-line options. Olanzapine, lithium or valproate plus antidepressant are also considered first-choiche treatments. In order to prevent relapses lithium, lamotrigine, valproate or atypical antipsychotics are recommended [63].

References

1. Borri C, Mauri M, Oppo A, Banti S, Rambelli C, Ramacciotti D. et. al. *Axis I psychopathology and functional impairment at the third month of pregnancy: results from the Perinatal Depression – Research and Screening Unit (PND-ReScU) study*. J. Clin. Psychiatry 2008; 69(10): 1617–1624.
2. Andersson L, Sundstrom-Poromaa I, Wulff M Aström M, Bixo M. *Depression and anxiety during pregnancy and six months postpartum: a follow up study*. Acta Obstet. Gynecol. Scand. 2006; 85(8): 937–944.
3. Heron J, Haque S, Oyebode F Craddock N, Jones I. *A longitudinalstudy of hypomania and depression symptoms in pregnancy and the postpartum period*. Bipolar Disord. 2009; 11(4): 410–417.
4. Vesga-Lopez O, Blanco C, Keyes K, Olfson M, Grant BF, Hasin DS. *Psychiatric disorders in pregnant and postpartum women in the United States*. Arch. Gen. Psychiatry 2008; 65(7): 805–815.
5. Newport DJ, Stowe ZN, Viguera AC, Calamaras MR, Juric S, Knight B. et. al. *Lamotrigine in bipolar disorder: Efficacy during pregnancy*. Bipolar Disord. 2008; 10: 432–436.
6. Grof P, Robbins W, Alda M, Berghoefer A, Vojtechovsky M, Nilsson A. et. al. *Protective effect of pregnancy in women with lithium-responsive bipolar disorder*. J. Affect. Disord. 2000; 61(1–2): 31–39.
7. Bergink V, Bouvy PF, Vervoort JS, Koorengevel KM, Steegers EA, Kushner SA. *Prevention of postpartum psychosis and mania in women at high risk*. Am. J. Psychiatry 2012; 169(6): 609H15.
8. Bodén R, Lundgren M, Brandt L, Reutfors J, Anderson M, Kieler H. *Risks of adverse pregnancy and birth outcomes in women treated or not treated with mood stabilisers for bipolar disorder: population based cohort study*. BMJ 2012; 345: e7085.
9. Galbally M, Snellen M, Lewis AJ. *A review of the use of psychotropic medication in pregnancy*. Curr. Opin. Obstet. Gynecol. 201; 23(6): 408–414.
10. *Management of perinatal mood disorders. A national clinical guideline*. Edinburgh, Scotland: Scottish Intercollegiate Guidelines Network; 2012.
11. Yacobi S, Ornoy A. *Is lithium a real teratogen? What can we conclude from the prospective versus retrospective studies*? Isr. J. Psychiatry Relat. Sci. 2008; 45(2): 95–106.
12. Dodd S, Berk M. *The safety of medications for the treatment of bipolar disorder during pregnancy and the puerperium*. Curr. Drug Saf. 2006; 1: 25–33.
13. Oyebode F, Rastogi A, Berrisford G, Coccia F. *Psychotropics in pregnancy: safety and other considerations*. Pharmacol. Ther. 2012; 135: 71–77.

14. Jacobson SJ, Jones K, Johnson K, Ceolin L, Kaur P, Sahn D. et. al. *Prospective multicentre study of pregnancy outcome after lithium exposure during first trimester*. Lancet 1992; 339(8792): 530–533.

15. Bschor T, Bauer M. *Side effects and risk profile of lithim: critical assessment of a systematic review and meta-analysis*. Nervenarzt. 2013; 84(7): 860–863.

16. McKnight RF, Adida M, Budge K, Stockton S, Goodwin GM, Geddes JR. *Lithium toxicity profile: a systematic review and meta-analysis*. Lancet 2012; 379(9817): 721–728.

17. Gentile S. *Lithium in pegnancy: the need to treat, the duty to enure safety*. Expert Opin. Drug Saf. 2012; 11(3): 425–437.

18. Cohen LS, Friedman JM, Jefferson JW, Johnson EM, Weiner ML. *A reevaluation of risk of in utero exposure to lithium*. JAMA 1994; 271(2): 146–150.

19. Van der Lugt NM, van de Maat JS, van Kamp IL, Knoppert-van der Klein EA, Hovens JG, Walther FJ. *Fetal, neonatal and developmental outcomes of lithium-exposed pregnancies*. Early Hum. Dev. 2012; 88(6): 375–378.

20. Sabers A, Tomson T. *Managing antiepileptic drugs during pregnancy and lactation*. Curr. Opin. Neurol. 2009; 22: 157–161.

21. Bravo A, Hernandez D, Martinez-Villarreal L, Elizondo G, Esmer C. *Severe consequences of carbamazepine exposure in utero. BMJ Case Rep. 2011*.

22. Akar M, Dilli D, Yilmaz Y, Erdeve O, Oguz S, Uras N. et. al. *A case of fetal carbamazepine syndrome with right hemihypoplasia of the entire body*. Genet. Couns. 2012; 23(1): 19–24.

23. Włodarczyk BJ, Palacios AM, George TM, Finnell RH. *Antiepileptic drugs and pregnancy outcomes*. Am. J. Med. Genet. A. 2012; 158A(8): 2071–2090.

24. Jentink J, Dolk H, Loane MA, Morris JK, Wellesley D, Garne E. et. al. *Intrauterine exposure to carbamazepine and specific congenital malformations: systematic review and case-control study*. BMJ 2010; 341: c6581.

25. Campbell E, Devenney E, Morrow J, Russell A, Smithson WH, Parsons L. et. al. *Recurrence risk of congenital malformations in infants exposed to antiepileptic drugs in utero*. Epilepsia 2013; 54(1): 165–171.

26. Hernández-Díaz S, Smith CR, Shen A, Mittendorf R, Hauser WA, Yerby M. et. al. *Comparative safety of antiepileptic drugs during pregnancy*. Neurology 2012; 78(21): 1692–1699.

27. Vajda FJ, Graham J, Roten A, Lander CM, O'Brien TJ, Eadie M. *Teratogenicity of the newer antiepileptic drugs – the Australian experience*. J. Clin. Neurosci. 2012; 19(1): 57–59.

28. Vajda FJ, Horgan D, Hollingworth S, Graham J, Hitchcock AA, Roten A. et. al. *The prescribing of antiepileptic drugs for pregnant Australian women*. Aust. N. Z. J. Obstet. Gynaecol. 2012; 52(1): 49–53.

29. Holmes LB, Mittendorf R, Shen A, Smith CR, Hernandez Diaz S. *Fetal effects of anticonvulsivant polytherapies: different risks for different drug combination*. Arch. Neurol. 2011; 68810: 1275–1281.

30. Hill DS, Włodarczyk BJ, Palacios AM, Finnell RH. *Teratogenic effects of antiepileptic drugs*. Expert Rev. Neurother. 2010; 10(6): 943–959.

31. Vajda FJ, O'Brien TJ, Graham J, Lander CM, Eadie MJ. *Associations between particular types of fetal malformation and antiepileptic drug exposure in utero*. Acta Neurol. Scand. 2013; 128(4): 228–234.

32. Almgren M, Källén B, Lavebratt C. *Population-based study of antiepileptic drug exposure in utero-influence on head circumference in newborns*. Seizure 2009; 18(10): 672–675.

33. Pennell PB, Klein AM, Browning N, Baker GA, Clayton-Smith J, Kalayjian LA. et. al. *Differential effects of antiepileptic drugs on neonatal outcomes*. Epilepsy Behav. 2012; 24(4): 449–456.

34. Banach R, Boskovic R, Einarson T, Koren G. *Long-term developmental outcome of children of women with epilepsy, unexposed or exposed prenatally to antiepileptic drugs: a meta-analysis of cohort studies*. Drug Saf. 2010; 33(1): 73–79.

35. Nadebaum C, Anderson VA, Vajda F, Reutens DC, Barton S, Wood AG. *Language skills of school-aged children prenatally exposed to antiepileptic drugs*. Neurology 2011; 76(8): 719–726.

36. Cummings C, Stewart M, Stevenson M, Morrow J, Nelson J. *Neurodevelopment of children exposed in utero to lamotrigine, sodium valproate and carbamazepine*. Arch. Dis. Child. 2011; 96(7): 643–647.

37. Galbally M, Roberts M, Buist A, Perinatal Psychotropic Review Group. *Mood stabilizers in pregnancy: a systematic review*. Aust. N. Z. J. Psychiatry 2010; 44(11): 967–977.

38. Ozkan H, Cetinkaya M, Köksal N, Yapici S. *Severe fetal valproate syndrome: combination of complex cardiac defect, multicystic dysplastic kidney, and trigonocephaly*. J. Matern. Fetal Neonatal Med. 2011; 24(3): 521–524.

39. Tomson T, Battino D, Bonizzoni E, Craig J, Lindhout D, Sabers A. et. al. *Dose-dependent risk of malformations with antiepileptic drugs: an analysis of data from the EURAP epilepsy and pregnancy registry*. Lancet Neurol. 2011; 10(7): 609–617.

40. Vajda FJ, Graham JE, Hitchcock AA, O'Brien TJ, Lander CM, Eadie MJ. *Is lamotrigine a significant human teratogen? Observations from the Australian Pregnancy Register*. Seizure 2010; 19(9): 558–561.

41. Koo J, Zavras A. *Antiepileptic drugs (AEDs) during pregnancy and risk of congenital jaw and oral malformation*. Oral Dis. 2012; 19(7): 712–720 .

42. Meador KJ, Baker GA, Browning N, Cohen MJ, Bromley RL, Clayton-Smith J. et. al. *Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study*. N. Engl. J. Med. 2009; 360(16): 1597–1605.

43. Meador KJ, Baker GA, Browning N, Cohen MJ, Bromley RL, Clayton-Smith J. et. al. *Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study*. Lancet Neurol. 2013; 12(3): 244–252.

44. Shallcross R, Bromley RL, Irwin B, Bonnett LJ, Morrow J, Baker GA. et. al. *Child development following in utero exposure: Levetiracetam vs. sodium valproate*. Neurology 2011; 76: 383–389.

45. Meador KJ, Baker GA, Browning N, Cohen MJ, Clayton-Smith J, Kalayjian LA. et. al. *Foetal antiepileptic drug exposure and verbal versus non-verbal abilities at three years of age*. Brain 2011; 134(2): 396–404.

46. Christensen J, Gronborg TK, Sorensen MJ, Schendel D, Parner ET, Pedersen LH. et. al. *Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism*. JAMA 2013; 309(16): 1696–1703.

47. Cunnington M, Tennis P. *Lamotrigine and the risk of malformations in pregnancy*. Neurology 2005; 64: 955–960.

48. Cunnington MC, Weil JG, Messenheimer JA, Ferber S, Yerby M, Tennis P. *Final results from 18 years of the International Lamotrigine Pregnancy Registry*. Neurology 2011; 76(21): 1817–1823.

49. Vajda FJ, Hitchcock AA, Graham J, O'Brien TJ, Lander CM, Eadie MJ. *The teratogenic risk of antiepileptic drug polytherapy*. Epilepsia 2010; 51(5): 805–810.

50. Mølgaard-Nielsen D, Hviid A. *Newer-generation antiepileptic drugs and the risk of major birth defects*. JAMA 2011; 305(19): 1996–2002.

51. Green MW, Seeger JD, Peterson C, Bhattacharyya A. *Utilization of topiramate during pregnancy and risk of birth defects*. Headache 2012; 52(7): 1070–1084.

52. Uludag S, Aydin Y, Yilmaz O, Aksoy F, Bakkaloglu D, Sen C. *Multiple fetal anomalies in association with topiramate and oxcarbezepine treatment*. Fetal Pediatr. Pathol. 2012; 31(3): 154–158.

53. Rihtman T, Parush S, Ornoy A. *Preliminary findings of the developmental effects of in utero exposure to topiramate*. Reprod. Toxicol. 2012; 34(3): 308–311.

54. Fujii H, Goel A, Bernard N, Pistelli A, Yates LM, Stephens S. et. al. *Pregnancy outcomes following gabapentin use: Results of a prospective comparative cohort study*. Neurology 2013; 80(17): 1565–1570.

55. Holmes LB, Hernandez-Diaz S. *Newer anticonvulsants: lamotrigine, topiramate and gabapentin*. Birth Defects Res. A. Clin. Mol. Teratol. 2012; 94(8): 599–606.

56. Petrenaite V, Sabers A, Hansen-Schwartz J. *Seizure deterioration in women treated with oxcarbazepine during pregnancy*. Epilepsy Res. 2009; 84(2–3): 245–249.

57. Montouris G. *Safety of the newer antiepileptic drug oxcarbazepine during pregnancy*. Curr. Med. Res. Opin. 2005; 21(5): 693–701.

58. Viguera AC, Whitfield T, Baldessarini RJ, Newport DJ, Stowe Z, Reminick A. et. al. *Risk of recurrence in women with bipolar disorder during pregnancy: prospective study of mood stabilizer discontinuation*. Am. J. Psychiatry 2007; 164(12): 1817–1824.

59. National Institute for Health and Clinical Excellence, NICE. *Bipolar Disorder: the Management of bipolar disorder in Adults, Children and Adolescent, in Primary and Secondary Care. NICE clinical guidelines 38*. 2006. Available at http://guidance.nice.org.ok/CG38 (access 31 august 2014)

60. *ACOG Practice Bulletin: Clinical management guidelines for obstetrician-gynecologists number 92, April 2008 (replaces Practice Bulletin number 87, November 2007). Use of psychiatric medication during pregnancy and lactatio*n. Obstet. Gynecol. 2008; 111: 1001–1020.

61. Grunze H, Vieta E, Goodwin GM, Bowden C, Licht RW, Möller HJ. et. al. *The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders: Update 2012 on the long-term treatment of bipolar disorder*. World J. Biol. Psychiatry 2013; 14: 154–219.

62. Goodwin GM. Consensus Group of the British Association for Psychopharmacology. *Evidence-based guidelines for treating bipolar disorder: revised second edition – recommendations from the British Association for Psychopharmacology*. J. Psychopharmacol. 2009; 23(4): 346–388.

63. Yatham LN, Kennedy SH, Parikh SV, Schafer A, Beaulieu S, Alda M. et. al. *Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines of the management of patients with bipolar disorder: update 2013*. Bipolar Disord. 2013; 15: 1–44.

Address: Giulia Costoloni
Division of Psychiatry, Department of Molecular Medicine,
University of Siena, School of Medicine
Italy, 53100 Siena, Viale Bracci 1