

The Safety of Medications for the Treatment of Bipolar Disorder During Pregnancy and the Puerperium

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Abstract: Risks associated with pharmacological treatment of bipolar disorder are heightened during reproductive events. Treatments need to be planned with the mutual agreement of both the treating physician and the patient and tailored to the needs of the individual so as to minimise risk while providing adequate treatment. Conventional treatments have all been associated with teratogeny in first trimester exposure, lithium with cardiac malformation and valproate and carbamazepine with neural tube malformations. There have been an insufficient number of first trimester exposures to the newer anticonvulsant mood stabilisers, lamotrigine and oxcarbazepine, to determine whether there is a safety advantage in switching to these agents. Increasingly, atypical antipsychotics are being suggested as useful agents for the treatment of bipolar disorder. While not known to be teratogenic, there are other reproductive safety concerns associated with these agents. Bipolar disorder patients may be prescribed antidepressants, and many of these agents are associated with a low safety risk during reproductive events, however data regarding use of these agents are currently equivocal. Adverse outcomes from inadequate pharmacological prophylaxis have been documented for both the mother and the baby. Risks and benefits need to be carefully balanced based on an accurate review of the evidence.

Keywords: Bipolar disorder, mood stabilisers, pregnancy, puerperium, lithium, anticonvulsant, teratogenicity.

1. INTRODUCTION

Though there are many medications from a diverse range of psychotropic drug classes which are used routinely for the treatment of bipolar disorder, only a handful of these medications have proven efficacious in the prevention of relapse of episodes of mania or depression. The most well know of these mood stabilisers, lithium, carbamazepine and valproate, have all been associated with concerns regarding teratogenicity. The safety in pregnancy of the newer anticonvulsant mood stabilisers lamotrigine and oxcarbazepine [1] is poorly characterised.

Antipsychotic agents as a class have been demonstrated to be of value in the treatment of acute mania. There is less data in the treatment of other phases of bipolar illness, with data of efficacy of quetiapine and olanzapine in the management of depression, and data for maintenance treatment with olanzapine and aripiprazole, although data are likely to be forthcoming for other atypical agents in these phases [2].

Other psychotropic drugs used in the treatment of bipolar disorder have efficacy in the treatment of acute episodes of illness or for the treatment of specific symptoms. Antidepressants, for example, may be used for the treatment of acute depressive episodes, although their use in maintenance, is controversial [3]. Other agents, such as benzodiazepines, may be used to treat insomnia or anxiety secondary to bipolar disorder. Symptoms of anxiety are

common during pregnancy and may require treatment. A child-bearing related onset of psychiatric illness is associated with a greater frequency of anxiety disorders than in women whose onset of psychiatric illness is not related to child bearing [4].

When a woman with bipolar disorder is considering becoming pregnant, it is strongly recommended that a treatment and monitoring plan be negotiated between the woman and her treating physician ideally prior to conception [1]. The treatment plan should balance the needs of the woman in managing her bipolar illness with the risks to the foetus from the medications. Strategies to minimise the risk of damage to the foetus should be used. The goal of treatment should be to adequately manage the bipolar illness while minimising risks to the foetus.

Planning treatment can be problematic as all of the conventional mood-stabilisers, the corner stones of any treatment of bipolar disorder, have been associated with potential risk to the developing foetus. As it is precisely these agents, which provide the most reliable prophylaxis against illness relapse, they have the least flexibility in their usage within the treatment plan. Ceasing these medications is sometimes suggested during the most critical times of the pregnancy, organogenesis in the first trimester and immediately prior to parturition, however this practise is associated with a risk of illness relapse which can only partially be estimated from the patient's history.

When considering the risks to the foetus from individual agents it must be recognised that agents are not of equal importance for the treatment of bipolar disorder.

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2. CONVENTIONAL MOOD-STABILISERS

The use of lithium, valproate and carbamazepine during pregnancy is associated with significant risks and has been well documented. Many women have been exposed to these agents during pregnancy and some of these exposures resulted in teratogenic consequences. Risks associated with exposure to these agents can be calculated.

2.1. Lithium

Lithium is administered by oral dosing as a carbonate salt. It has a narrow therapeutic window with serum concentrations between 0.8 and 1.0 mmol/L required for effective treatment without unacceptably high risks of adverse effects. Lithium is eliminated by renal clearance. In a study of 79 inpatients with normal renal function the mean lithium volume of distribution was 32.8 L and mean lithium clearance was 1.36 L/hr. The most significant variables effecting lithium pharmacokinetics were lean body mass and creatinine clearance [5].

Lithium pharmacokinetics is altered during pregnancy. The glomerular filtration rate (GFR) increases by 50%, renal perfusion increases in early pregnancy by 75% and declines in late third trimester. The GRF returns to pre-pregnancy levels soon after parturition [6]. Adjusting the dose of lithium proportional to the change in GRF is required to maintain the serum concentration at pre-pregnancy levels. Gastrointestinal changes with pregnancy, decreased gastric acidity and increased transit time, have not been reported to significantly alter the pharmacokinetics of lithium.

Lithium has been associated with teratogenicity and foetal toxicity in laboratory animals and in humans. High incidences of malformations were produced by dosing pregnant mice [7] and rats [8, 9] with lithium at high doses (up to 200 mg/kg, oral or intraperitoneal), and included eye defects, external ear defects, deformed bones and cleft palate. Auricular abnormalities have been reported in a baby exposed *in utero* to lithium [10], however of greater concern with human *in utero* exposure are well documented reports of cardiac malformations, in particular Ebstein's anomaly of the tricuspid valve [11-15]. The risk of cardiac malformation from *in utero* exposure to therapeutic levels of lithium has been estimated as 1 in 1000 [13].

Exposure to lithium *in utero* may cause foetal intoxication throughout gestation, with risks of adverse outcomes greatest at parturition. Embryotoxicity was produced in pregnant Wistar rats administered lithium carbonate and included a reduction in weight and number of pups [9]. Therapeutic levels of lithium in humans have not been associated with increases in stillbirths or spontaneous abortions. Some evidence suggests that *in utero* lithium exposure may be associated with premature birth, macrosomia and increased perinatal mortality [16]. A study from the International Register of Lithium Babies, which is a voluntary register and may have a selection bias, showed that 36% of infants were born prematurely, 37% of pre-term infants were large for their gestational age and 15% of full-term infants were large for their gestational age [17]. A neonatal syndrome, named "floppy baby syndrome" [14, 18], manifests as cyanosis and lethargy [19] and is of significant concern. Thyroid toxicity is reported at significant frequency

[14, 20-22]. Also reported in the neonate are; nephrogenic diabetes insipidus [23, 24], gross functional lesions of the cardiovascular, renal and neuromuscular systems [25], pulmonary vascular resistance [26], hypotonia, poor feeding and weak startle reflex [22]. Risk of neonatal toxicity can be reduced through management techniques such as tapering off lithium for parturition [27].

A follow-up study of 60 children who were exposed *in utero* to lithium and had no malformations at birth, matched against their non-exposed siblings, showed no increase in the frequency of physical or mental anomalies amongst the lithium exposed children [28].

2.2. Valproate

Valproate is administered by oral dose either as sodium valproate or in the dimer form as divalproex sodium. Both forms dissociate to valproate ions in the gastrointestinal tract and do not differ after systemic absorption. Many varying formulations of monomer and dimer are available.

Valproate is 90% protein bound in plasma, which includes 60% binding to albumin, and shows non-linear pharmacokinetics as albumin binding sites become saturated at higher doses. During pregnancy plasma albumin decreases in the mother and free fatty acid levels can also vary. Maternal free fractions of valproate increase from 10% during early pregnancy to 20% at full term [29]. Foetal accumulation of valproate and two of its metabolites has been measured from paired maternal/foetal blood samples and is attributed to changes in maternal plasma proteins [30]. Formulations and dosing regimens that produce higher concentration maxima may be at increased risk of saturated maternal albumin binding, suggesting a need for divided dosing and caution with high doses.

Valproate has been associated with teratogenic and toxic outcomes from foetal exposure. Of major concern are the neural tube malformations, which may result from first trimester exposure. This malformation is suggested to be caused by an increase in free radical burden associated with the metabolite valproate-4-ene, while also reducing the efficacy the free radical scavenger enzyme activity by depleting selenium required for glutathione peroxidase synthesis [31]. Increased teratogenic outcomes with increased maternal dose has been demonstrated in a primate model [32]. Reported neural tube defects have included; spina-bifida [33] and hydrocephalus and meningomyelocele [34]. Other severe malformations have been reported from *in utero* valproate exposure and include skeletal abnormalities and microcephaly [35], septo-optic dysplasia [36], and congenital heart defects [37, 38]. Risk of limb defects due to valproate exposure was calculated as 0.42% using data from 22,294 consecutive malformed infants from the Spanish Collaborative Study of Congenital Malformations [39]. In a survey of 149 births from the North American Antiepileptic Drug Pregnancy Registry, 16 cases of malformations were identified (10.7%), whereas the prevalence of malformations in a control group of neonates not exposed *in utero* to anticonvulsant medication was 1.62% [40]. In an Australian study of 307 first trimester exposures to antiepileptic medications, the incidence of birth defects was 16.7% for valproate exposure (N=103 exposures), 7.7% for lamotrigine exposure (N=68 exposures) and 3.3% for carbamazepine

exposure (N=144 exposures), suggesting that valproate is associated with a greater risk to the foetus than other anticonvulsant medications or lithium [41].

Also of note is that *in utero* valproate exposure, termed 'foetal valproate syndrome', has been well documented to produce a consistent facial appearance, several other characteristic anomalies and dysfunction of the central nervous system. Facial features can include epicanthic folds, a flat nasal bridge, small nose and anteverted nostrils, a long thin upper lip and thickened lower lip [42]. Gum hypertrophy and hypertrichosis [43] and ocular abnormalities [44] have also been associated with valproate exposure. Limb defects such as club feet and club hands may occur [43].

Case reports of foetal intoxication from valproate exposure have included afibrinogenemia [45], hypoglycaemia [37] and two fatal cases of liver atrophy and cholestasis in siblings [46]. Intrauterine haemorrhage has also been reported [47].

In a study of neuropsychological development, 249 children from mothers with epilepsy aged between 6 and 16 and their mothers (N=163) underwent a battery of neuropsychological tests. Forty-one children had been exposed *in utero* to sodium valproate monotherapy, 52 to carbamazepine monotherapy, 76 to other anticonvulsants or polytherapy and 80 were not exposed to any anticonvulsant. Valproate exposure was associated with a lower verbal IQ in these children. The odds ratio for a verbal IQ score less than 69 was 1.00 in non-exposed children, 1.03 in carbamazepine exposed children and 3.47 in valproate exposed children suggesting that the harmful effects of valproate exposure *in utero* may extend into childhood neurodevelopment [48].

2.3. Carbamazepine

Carbamazepine is administered by oral dose and is available in several formulations, which vary in absorption characteristics from the gastrointestinal tract. Carbamazepine binds to albumin and alpha-1-acid glycoprotein. During pregnancy plasma protein levels decrease effecting total blood carbamazepine concentrations, however studies have shown that the free fraction concentration of carbamazepine in plasma does not vary significantly with pregnancy [49]. Carbamazepine is both a substrate and inducer of CYP3A4. Carbamazepine has been shown not to induce CYP3A4 in the human placenta [50], however transplacental exposure to carbamazepine has been associated with an decrease in vitamin K [51] and folate [31] in the foetus, presumably due to enzyme induction. Carbamazepine and three metabolites have been measured in cord blood and compared to maternal serum concentrations. Results showed no evidence of foetal accumulation for carbamazepine or its metabolites [50].

Carbamazepine has been associated with teratogenic and toxic outcomes associated with foetal exposure. Possible carcinogenicity of carbamazepine, suggested in a case report of congenital neuroblastoma [52], is not supported by substantial data. The teratogenicity has been associated with the formation of an oxidised metabolic intermediate, carbamazepine -10,11-epoxide. Several enzyme pathways, including epoxide hydrolase and glutathione transferase, can clear the epoxide. It is likely that these enzymes can be induced by carbamazepine. A study has demonstrated that

polypharmaceutic combinations, including addition of valproate, can increase levels of the epoxide intermediate [53]. Pooled data from 984 births with *in utero* exposure to carbamazepine, with no exposures to combined valproate and carbamazepine included, identified nine cases of spina bifida. This suggests a risk of approximately 1%, which is higher than the expected population prevalence of spina bifida of 0.07% [54]. Other malformations reported with carbamazepine exposure have included congenital rib abnormalities [55], minor craniofacial defects and fingernail hypoplasia [56] and cardiovascular and urinary tract anomalies and cleft palate [57]. Other reports of outcomes of carbamazepine exposure have included transient cholestatic hepatitis in a neonate [58] and reduced gestational age at delivery [57].

A study of 80 children exposed *in utero* to anticonvulsant found an association between deficits in IQ and minor malformations, suggesting that infants with minor malformations due to anticonvulsant exposure, including carbamazepine, may be at increased risk of below average neuropsychological development [59].

2.4. Oxcarbazepine

Oxcarbazepine, administered as an oral tablet or liquid, is completely absorbed in the gastrointestinal tract and extensively metabolised to its pharmacologically active metabolite 10-hydroxy-10,11-dihydrocarbamazepine (10-monohydroxy derivative MHD). Although it is a structural analogue of carbamazepine, oxcarbazepine and carbamazepine have different metabolic profiles [60]. Oxcarbazepine does not have an epoxide metabolite and does not auto-induce its own metabolism [61]. Consequently, oxcarbazepine appears to have a better tolerability and safety profile than carbamazepine. MHD is 40% protein bound [60], suggesting that changes in plasma protein concentrations during pregnancy are unlikely to impact on the pharmacokinetics of oxcarbazepine. The systemic elimination rate of MHD is determined by the rate of renal clearance and dose adjustment is required for impaired renal function [62]. Whether increased renal clearance during pregnancy influences the pharmacokinetics of MHD in a clinically significant way has not been reported.

Studies with perfused human placenta have demonstrated rapid passage of oxcarbazepine and slower passage of MHD. Oxcarbazepine was metabolised to MHD in the placenta [50]. Oxcarbazepine, MHD and another metabolite 10,11-trans-dihydroxy-10,11-dihydrocarbamazepine have been detected in cord blood and measured at similar concentrations to those found in paired maternal specimens [50, 63, 64].

An insufficient number of *in utero* exposures to oxcarbazepine have been reported to determine its risk during pregnancy. In a report of 12 exposures there were 3 spontaneous abortions and 9 normal outcomes [65]. A larger study reported 55 *in utero* exposures to oxcarbazepine, 35 as monotherapy and 25 as combination therapy. A cardiac malformation was reported in one neonate exposed to oxcarbazepine in combination with phenobarbital [66].

3. NEWER ANTICONVULSANT MOOD-STABILISERS

Knowledge of the safety of newer agents during pregnancy is always hindered by a paucity of information. Too few women have yet been exposed to lamotrigine and oxcarbazepine during pregnancy for these agents to be fully evaluated, however valuable new information on the safety during pregnancy of lamotrigine has recently been reported.

3.1. Lamotrigine

Lamotrigine, administered as an oral tablet, is rapidly absorbed from the gastrointestinal tract reaching a peak plasma concentration in 1 to 4 hours. It is 55% plasma protein bound [67]. There is no evidence that plasma protein changes during pregnancy significantly effects the plasma concentration of lamotrigine. The principal clearance mechanism of lamotrigine is by hepatic glucuronidation to produce 5-N and 2-N glucuronide metabolites [68].

An observational study of 16 pregnancies in 14 women treated with lamotrigine, with blood specimens collected prior to conception, during all three trimesters and post-partum for 7 of the pregnancies and incomplete data for the other pregnancies, demonstrated that mean lamotrigine clearance increases by > 50% during pregnancy and quickly returns to pre-pregnancy rates post-partum. Clearance peaked in second and third trimesters. Considerable variation in changes in apparent clearance of lamotrigine was measured between individuals and throughout the course of the pregnancy within the same individual [69]. Another lamotrigine monotherapy study of twelve pregnancies confirmed the considerable inter and intra-individual variation and calculated that lamotrigine plasma level to dose ratios may decrease to 47% of levels measured prior to pregnancy [70]. A further study of 14 pregnant women treated with lamotrigine monotherapy found that lamotrigine apparent clearance progressively increased during pregnancy, peaking at 361.2% of pre-pregnancy levels at 32 weeks of gestational age, then slowly declining but remaining high until parturition. Toxicity due to high plasma concentrations of lamotrigine in the first two weeks post-partum, as clearance returned to pre-pregnancy rates, was reported by several study participants [71]. This suggests that lamotrigine plasma levels should be measured prior to conception and monitored throughout pregnancy and post-partum until clearance rates return to pre-pregnancy levels. Dose adjustments required to maintain the lamotrigine plasma concentration at steady-state should be calculated on a per individual basis.

Lamotrigine has not been documented to cause teratogenic outcomes, however many more exposures will need to be reported before the safety of lamotrigine in pregnancy can be fully assessed. Twelve major congenital malformations have been reported from 414 first trimester exposures to lamotrigine monotherapy recorded on the International Lamotrigine Pregnancy Register. The percentage of malformations recorded on the register (2.9%) was within the expected range for malformations from pregnancies in the general population not exposed to anticonvulsant medication (2-3%). There was no distinctive pattern amongst the birth defects recorded. There were 88 first trimester exposures to lamotrigine in combination with

valproate with 11 major malformations reported (12.5%) and 182 first trimester exposures to lamotrigine in combination with medications other than valproate with 5 major malformations reported (2.7%) [72, 73]. In a Danish study of 51 pregnancies exposed to lamotrigine *in utero*, 1 minor malformation was reported (2%) [74]. In a UK study of 476 pregnancies exposed to lamotrigine *in utero* the rate of major congenital malformations was 2.9% [75].

Rapid transplacental passage of lamotrigine has been demonstrated by human placental perfusion studies. Analysis of paired specimens showed a cord to maternal lamotrigine plasma concentration ratio of 1.02 and 1.55 in two pairs of specimens [76]. A paired cord to maternal lamotrigine plasma concentration ratio of 1.2 was reported in a case study [77]. No reports of serious adverse effects in neonates attributable to lamotrigine could be identified, in spite of clear evidence to suggest that levels of exposure to lamotrigine in neonates is considerable. Lamotrigine clearance in the neonate may be slow and lamotrigine levels in the neonate have been reported to remain high when an infant is re-exposed through breast-feeding [78].

A study of 62 children exposed *in utero* to lamotrigine and assessed at birth and at 1, 3 and 6 months and 1 year after birth measured Apgar score, weight, size, cranial parameters and psychomotor development. All findings were within the expected range for the general population [79].

4. ATYPICAL ANTIPSYCHOTICS

The efficacy of the various atypical antipsychotic agents in the treatment of bipolar disorder has not been investigated with the same thoroughness for each agent, therefore it is not yet possible to evaluate whether the utility of atypical antipsychotic agents is specific to individual agents or represents a 'class effect'. Many antipsychotic agents are well documented for their efficacy in the treatment of acute episodes of mania [2]. Quetiapine and olanzapine have also been shown to be effective in treating the depressive phase of bipolar illness and olanzapine and aripiprazole have been demonstrated to be effective in maintenance treatment [2, 80].

In general, atypical antipsychotic agents have a better safety record when used during pregnancy than the conventional mood stabilisers. In a study of 151 pregnancies exposed to monotherapies or combination therapies with olanzapine (N=60), risperidone (N=49), quetiapine (N=36) and clozapine (N=6) there were 110 live births, 22 spontaneous abortions, 15 therapeutic abortions and 4 stillbirths. Major malformations were reported in a neonate exposed to olanzapine and included cleft lip, encephalocele and aqueductal stenosis. A rate of 1 malformation in 151 exposures suggests that these agents are not associated with an increased risk for major malformations. Mean gestational age at birth and birth weight was not effected by drug exposure [81]. More data is clearly required before safety can be assumed.

Atypical antipsychotic agents are often used in combination with conventional mood stabilisers. Polytherapy is associated with increased risks of adverse outcomes with pregnancy [65]. Risperidone and clozapine are metabolised by CYP3A4 and in combination therapy there may be a

Table 1. Adverse Effects to the Foetus of Mood-Stabilisers

Drug	Foetal malformations (1 st trimester)	Foetal toxicity	Changes in use
Lithium	Cardiac malformation	“floppy baby”	Consider not using lithium in 1 st trimester and perinatally
Valproate	Neural tube malformations, foetal valproate syndrome	foetal intoxication	Consider not using valproate in 1 st trimester and perinatally
Carbamazepine	Neural tube malformations	Case reports of toxicity	Consider not using carbamazepine in 1 st trimester
Lamotrigine	Some data suggesting that malformations are unlikely	No serious adverse events reported	Insufficient data
Oxcarbazepine	Insufficient data	Insufficient data	Insufficient data for 1 st trimester use, consider not using perinatally (somnolence)
Olanzapine	No evidence to suggest an association with malformations	Possible association with low birth weight	Insufficient data for 1 st trimester use, consider not using perinatally (somnolence)
Aripiprazole	Insufficient data	Insufficient data	Insufficient data
Quetiapine	Insufficient data	Insufficient data	Insufficient data

pharmacokinetic interaction between these agents and carbamazepine, which is an inducer of CYP3A4.

5. OTHER MEDICATIONS

Sufferers of bipolar disorder are often treated with multiple medications, often involving a mood stabiliser as primary treatment and other medication for the treatment of specific symptoms or acute episodes. Some of these other agents are associated with specific risks when used during pregnancy.

5.1. Antidepressants

Antidepressants are used for the treatment of acute depressive episode of bipolar disorder, however they are associated with a risk of manic switch, rapid cycling and uncertain efficacy in maintenance [1]. The relative safety of antidepressants during pregnancy has been established through many thousands of exposures and they are not associated with an increased risk for malformations [82]. A review of records found no association between *in utero* exposure to tricyclic antidepressants (TCAs) (N=209) or Selective Serotonin Reuptake Inhibitors (SSRIs) (N=185) and either congenital malformations or developmental delay, however SSRIs were associated with earlier delivery and lower birthweight and lower Apgar scores [83]. It has been suggested that antidepressant use may be associated with an increased risk of spontaneous abortion [84] and a neonatal withdrawal syndrome with antidepressant exposure, especially to paroxetine, has been identified [85]. The effect, if any, of *in utero* antidepressant exposure on neurocognitive development is controversial [86]. A prospective study assessed children who had been exposed *in utero* to TCAs (N=46), fluoxetine (N=40) and children from mothers with no history of depression and no exposure to antidepressants (N=36). Antidepressant exposure had no effect on children's global IQ, language development or behaviour, however greater duration of maternal depression was associated with low infant IQ and a greater number of episodes of maternal depression was associated with poor infant language development [87].

5.2. Benzodiazepines

Benzodiazepines may be administered to bipolar patients for symptomatic control of anxiety, agitation and insomnia. In a study of 475 sufferers of bipolar disorder, the prevalence of any comorbid anxiety disorder was 30.5% for a current episode and 51.2% for having experienced an episode currently or previously [88], suggesting significant overlap between the two disorders.

Benzodiazepines vary significantly in their pharmacokinetic profiles. Clearance can be through phase I, phase II or phase I and II metabolic pathways. Changes in rates of benzodiazepine elimination due to pregnancy have not been documented. Benzodiazepines rapidly cross the placenta and are taken up by the foetus [89].

Benzodiazepine exposure *in utero* has been associated with teratogenicity, however several studies have reported contradictory findings. Interference with palatal closure has been demonstrated in animal studies [90] and an association between benzodiazepines and facial cleft malformations has been suggested for humans [91]. Negative results have been reported in prospective studies investigating the teratogenicity of human exposure with diazepam [92, 93], alprazolam [93-95], oxazepam [93], lorazepam [93], clonazepam [95, 96], medazepam [95], tofisopam [95] and nitrazepam [95] suggesting that the risk of malformation with first trimester exposure to benzodiazepines at therapeutic doses is minimal to low.

Perinatal use of benzodiazepines has been associated with ‘floppy infant syndrome’, which is characterised by sedation, hypotonia, hypothermia and low Apgar scores [97]. Signs of withdrawal symptoms in neonates exposed *in utero* to benzodiazepines are hypertonia, hyperreflexia, irritability, seizures, bradycardia and cyanosis. Withdrawal symptoms are reportedly initially more severe but less protracted for shorter acting benzodiazepines [98]. There is no data to suggest that benzodiazepine exposure may affect birth weight or length of gestation.

Table 2. Changes in Mood-Stabiliser Dosage During Pregnancy to Maintain Pre-Pregnancy Plasma Levels

Drug	Pharmacokinetic changes	Changes in dosage
Lithium	Increased renal clearance	Increase dosage by 50% to maintain pre-pregnancy serum levels
Lamotrigine	Increased metabolic clearance	Monitor serum levels and adjust dosage accordingly
Valproate	Changes in protein bound fraction in plasma	Avoid high concentration peaks
Carbamazepine	No significant changes	Not required
Oxcarbazepine	Insufficient data	Insufficient data
Olanzapine	Insufficient data	Insufficient data
Aripiprazole	Insufficient data	Insufficient data
Quetiapine	Insufficient data	Insufficient data

Neurodevelopment of infants exposed *in utero* to benzodiazepines has been investigated in several studies, though the results are not conclusive. A prospective study comparing 29 non-exposed infants with 17 infants who had been exposed *in utero* to benzodiazepines throughout pregnancy associated benzodiazepine exposure with a general delay in mental development [99]. In a much larger study of 550 children, who were followed longitudinally until they were up to four years of age, no increase in either the malformation rate or adverse effects on neurobehavioural development and IQ was detected. Some of children demonstrated below average development during the first year or so, but most had developed normally by four years of age. A review, without meta-analysis, of 41 studies reported no evidence of long term neurobehavioural sequelae from benzodiazepine exposure [100]. A role of benzodiazepine exposure in persistent developmental deficits could not be determined [97].

6. TREATMENT OPTIONS

A variety of pharmacological options are available for the management of bipolar disorder. Some of these have fairly clearly documented risks, while others have a lower risk profile in pregnancy. The treating physician will need to consider the consequences if medications are reduced or withdrawn to reduce the risk of harm to the foetus and neonate if exposed to pharmacological agents used to adequately treat the mother's bipolar illness. Several strategies are available to be pursued, some of which are applicable generally and some which need to be tailored to the individual.

If a woman with bipolar disorder is considering becoming pregnant a treatment plan between the patient and her treating physician should be agreed upon in frank and open discussions balancing risks and benefits and tailored to the individual needs of the patient. Of particular concern will be the choice of medications to administer during the first trimester and from gestational week 38 to parturition, however there are risks associated with medications at all stages of pregnancy.

Ceasing medications associated with teratogenicity from pre-conception until the end of the first trimester and tapering off medications from week 36 to 38 are controversial decisions, which may be considered for some women. The imperative to discontinue individual medications is clearly greater with some agents, such as valproate and carbamazepine. An obvious problem with

these strategies is that they are associated with an increased risk of relapse of bipolar illness. In a study of 42 women who discontinued lithium during pregnancy, 52% of women in this group experienced recurrence of their bipolar illness [101]. If women discontinue pharmacotherapy, an alternative treatment, such as psychotherapy, may be considered.

There are many practical obstacles to implementing these strategies. There is a high rate of unplanned pregnancy, which may be as high as 48% [102]. Discontinuing medications prior to conception may be problematic for couples who have difficulties conceiving. This can be particularly problematic for older couples. Women who remain episode free during the first trimester may be reluctant to resume pharmacotherapy for the remainder of their pregnancy. Stopping medication for parturition by tapering off may be beneficial when parturition occurs accurately at 40 weeks, but this does not always happen. Tapering off lithium for parturition has been associated with an increased number of induced labours [103].

Teratogenicity should be explained, ideally during pre-pregnancy planning and procedures for monitoring foetal development scheduled. Sensitivity towards the parent's attitude to therapeutic abortion is necessary and counselling should be provided if serious teratogenic drug effects are detected. Transabdominal ultrasound has a high degree of diagnostic accuracy for identifying certain malformations, however diagnostic accuracy will vary with abnormality and gestational age. Ultrasound investigations are often routinely conducted from 10 to 12 weeks of gestational age, but may be conducted later or repeated at 12 to 15 weeks, or even later. It is usually sufficient to schedule the number and timing of ultrasound procedures in accordance with local guidelines. Scheduling of additional procedures may be influenced by affordability, confidence in the findings from earlier procedures and the local legal status of therapeutic abortion at later stages of foetal development.

Maternal serum screening is routinely conducted and should be scheduled according to local guidelines. Raised levels of alpha-fetoprotein in maternal serum suggest an increased risk of neural tube malformations.

7. DISCUSSION AND CONCLUSION

Treatment decisions need to be made by balancing the risks and benefits of various treatment strategies, taking into consideration the requirements of the individual patient, however assessing risks and benefits may be a difficult and imprecise challenge. In particular, the risk of relapse

associated with altering medications will vary with the unique circumstances of each individual. Consequently it may be easier to make decisions concerning patients with long histories of severe recurrent illness, where continuing with treatment as usual may be prudent. Patients with good histories of stability with treatment may be more suitable candidates for modifying their treatment in order to minimise risks to the foetus, but good outcomes can be notoriously difficult to predict.

A risk from a "man-made" cause such as a drug, especially when the danger is an irreversible and very serious malformation, may be regarded as more worrying and less acceptable to the patient and sometimes also to health professionals, than a risk arising from a "natural" cause such as an illness. Consequently, even though the probability of relapse without pharmacological prophylaxis may be significantly greater than the probability of adverse outcomes from exposure of the foetus to therapeutic levels of these medications, the perception of risk from medications compared to risks from illness may be disproportionate. This is even more likely with an anxious patient, who may place excessive emphasis on risks from medications, even when those risks are remote [104].

Effectively managing the dilemmas imposed by treating bipolar disorder during pregnancy requires an understanding of the pharmacology of the medications used to treat bipolar illness, a clear understanding of bipolar illness itself, and frank, open and comprehensive discussions with the patient.

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