Perinatal Psychiatry Essay Prize for Medical Students

'Do you believe that the implications for the continuation of sodium valproate as a mood stabiliser in pregnancy are always worse than the risk of relapse of illness?'

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"Where subjects are predisposed to mental illness through either hereditary antecedents, previous illnesses, or through an excessive nervous susceptibility, pregnancy, delivery and lactation can have disastrous repercussions."

Louis-Victor Marcé (1858)

Louis-Victor Marcé of Paris, a key protagonist in early perinatal psychiatry, recognised that pregnancy and the puerperium have the potential to induce an exacerbation of mental illness, such as relapse of previously stable bipolar disorder. An antenatal deterioration of illness could result in a number of disinhibited behaviours that could harm mother and foetus. Additionally, a postpartum mood or psychotic episode could result in impaired attachment and neonatal development. As such, mood stabilisation is often seen as necessary during this period. Conversely, sodium valproate is a recognised teratogen with potentially devastating effects.

In order to determine which carries the greatest risk of harm, the author explores the impact of pregnancy on bipolar disorder, the recognised complications of sodium valproate, current national guidance and alternative interventions in lieu of valproate.

The impact of pregnancy and the puerperium on bipolar disorder and the indication for a mood stabilising agent.

Pregnancy carries with it the potential for great joy for a woman and her family and has consequently been viewed as a time of wellbeing, with some believing it has a protective effect on bipolar illness (Grof et al., 2000). However, it also brings a unique combination of physical, emotional and financial change. Whilst the aetiopathogenesis is yet to be fully understood, there is a consensus that pregnancy and the puerperium predispose to psychiatric illness, which has been documented as early as the mid-nineteenth century by Louis-Victor Marcé of Paris (Trede et al., 2009).

Freeman (2002) found through assessment of drug-naive women that the risk of recurrence of bipolar disorder and subsequent postpartum mood disturbance are 50% and 67% respectively. Furthermore, he notes that those women affected are likely to suffer similar problems in future pregnancies. Despite the problems with the retrospective methodology used and the small sample size, this conclusion warrants further exploration of the risk of untreated bipolar disorder (Heffner et al., 2013).

Viguera et al. (2007), acknowledging the need for a prospective analysis, assessed recurrence risk and time to recurrence among 89, initially euthymic

pregnant women who had chosen to either continue or discontinue mood-stabiliser treatment. They found that 70.8% of subjects experienced at least one episode of illness meeting DSM-IV criteria. Furthermore, they found that those who discontinued treatment spent over 40% of pregnancy in an illness episode, had a 2.3 times greater recurrence risk and more than 4 times shorter latency to new illness. Additionally, they noted that women who discontinued abruptly experienced a 50% risk of recurrence within two weeks, compared to those withdrawing gradually, who required 22 weeks to reach the same level of risk. This study further illustrates the impact that pregnancy can have upon maternal bipolar disorder and demonstrates that the gestational state responds sensitively to changes in mood stabilisation therapy.

One can intuitively understand that a relapse of illness can result in a range of behaviours from diminished self-care to more significantly harmful events such as alcohol or drug intoxication, resulting in a myriad of problems for mother and foetus. Investigations by Bodén et al. have found that untreated illness can result in an infant being born with a reduced APGAR score, as well as a series of metabolic problems. The most concerning of these was microcephaly and neonatal hypoglycaemia. Infants of untreated mothers were also found to be small for gestational age for weight, length and head circumference. However, this was suggested to be largely attributable to the use of tobacco and recreational drugs that has been previously associated with individual's suffering from bipolar disorder.

The aforementioned evidence illustrates that pregnancy, particularly in the absence of mood stabilisers, exposes women to an increased risk of relapse of bipolar illness, which can be detrimental to foetal development. However, the harm caused by untreated illness in pregnancy extends beyond bipolar disorder itself to a lack of education. Viguera et al. (2002) found that women are largely poorly informed about the relationship between bipolar disorder and pregnancy, and that GPs/psychiatrists had advised 45% of sampled patients with bipolar disorder against pregnancy. This may indicate that many pregnancies among those with bipolar disorder are unplanned, leaving a mother unprepared and unaware of the challenges her pregnancy may pose on her illness.

A review of the potential complications of valproic acid use during pregnancy.

Valproic acid, taken during pregnancy, crosses the placenta and has higher foetal than maternal concentrations. Decreased albumin in the maternal serum increases unbound valproate, which malignantly combines with an increased protein binding capacity of valproic acid in foetal serum (Nau et al., 1984). This process leads to a number of well-documented teratogenic effects and whilst the exact mechanism is unknown, early studies have linked these changes to decreased plasma zinc and selenium (Hurd et al., 1983).

According to Meador et al. (2008), valproate exposure in early pregnancy is associated with an approximately three-fold increase in major congenital malformations (~3% – 8-11%). The most common of these malformations are neural tube defects (NTD), usually lumbosacral defects that are both open and severe (Lindhout et al., 1992; Robert & Guibard, 1982). Iqbal et al. (2001) has corroborated these findings and suggests an estimated risk of spina bifida in children exposed to valproate gestationally of 1-2%, which is a 10-20-fold increase compared with the general population.

Distinctive patterns of minor anomalies of the facies and other organs have also been described in children born to women who used valproate during pregnancy (Iqbal et al., 2001; Christianson, 1994). These are collectively termed "foetal valproate syndrome" and are summarised in table 1.

Craniofacial abnormalities:	**Urogenital defects:**
• High forehead, microstomia.	• Hypospadias.
• Midface hypoplasia.	• Bilateral renal hypoplasia.
• Anteverted nostrils.	• Bilateral undescended testes.
• Short nose with a broad and/or flat nasal bridge.	**Skeletal:**
• Shallow philtrum.	• Long, thin, partly overlapping fingers and toes.
• Epicanthal folds.	• Hyperconvex nails.
• Small mouth with thin upper and thick lower lip.	• Defects of the radius**.**
• Micrognathia.	
• Flat orbits.	**Developmental delay:**
• Protruding eyes.	• Delay in speech.
• Low-set and rotated ears.	
• Hypertelorism.	**Respiratory tract anomalies.**
• Bulging frontal eminences.	
• Strabismus, nystagmus.	**Lumbosacral meningomyelocele.**
• Down-turned angles of mouth.	
• Thin upper vermilion border.	**Perinatal distress and unusual neonatal behaviour.**
• Cleft palate, cleft lip, club feet**.**	

Table 1: Summary of characteristic features of 'foetal valproate syndrome', adapted from Iqbal et al., 2001.

Less commonly reported complications of valproate use include clotting abnormalities. Valproate has been seen to induce depletion of vitamin K-dependent clotting factors I, II, VII, IX, X. Platelets and their aggregation were found to be similarly reduced (Iqbal et al., 2001). Furthermore there have been case reports of hepatic necrosis, cholestasis and hyperbilirubinaemia, which have also been previously documented in adults receiving this therapy (Iqbal et al., 2001; Dalens et al., 1980).

It has been noted above that untreated bipolar disorder can cause metabolic disturbance in the foetus. However, valproate treatment has also been shown to result in metabolic abnormalities, owed to the anabolic effects of the drug (Bond et al., 2009). This is supported by Bodén (2012) who found a correlation between in-utero valproate exposure and infants that were large for gestational age and hypoglycaemic post-delivery.

Cummings et al. (2011) conducted a large cohort study with children exposed to valproate monotherapy, showing that complications continue to develop post-natally. They found that the valproate group had an increased risk of delayed neurodevelopment compared with controls, when covariates were considered in analysis. This finding was elaborated on by Bromley et al (2014) who found that prenatal exposure to valproate is associated with approximately 8 point lower IQ scores in school aged children. Whilst the use of IQ measurements is historically controversial, Bromley et al. insist that this disparity was enough to cause impaired educational and occupational outcomes in later life. Furthermore, a study by Christensen et al. (2013) demonstrated that these developmental issues may present as autism spectrum disorder or childhood autism, with a three-fold increase in incidence among those with prenatal valproate exposure. This finding remained when the investigators controlled for the impact of epilepsy.

Like many of the studies cited in the literature, Christensen et al. (2013) have used subjects treated with valproate for epilepsy and not bipolar disorder. Whilst this neurological difference may be seen as inherently confounding, the commonest criticism of this generalisation is that the dose required for action as an anticonvulsant is much greater than that needed for mood stabilisation. As such, one could argue that valproate may be safe to use in lower doses. However, Tomson and Battino (2012) reviewed existing literature and found that the critical dose for valproate toxicity varied greatly. This indicates that if a safe antenatal dose does exist, it is currently unknown and the extensive aforementioned complications are too great a risk.

National guidance surrounding valproate use as a mood stabiliser in pregnancy.

Current guidelines (SIGN, 2012; NICE, 2014; McAllister-Williams et al., 2017) were reviewed by the author and revealed an unsurprising consensus against the use of sodium valproate as a mood stabiliser in pregnancy. They state that in view of early teratogenicity and longer term neurobehavioural toxicity, valproate should not be routinely prescribed for the management of acute or chronic mental illness in women or girls of childbearing potential (SIGN, 2012; NICE, 2014).

For those women who are already taking valproate, guidance encourages them to stop the drug due to the risk of foetal malformations and adverse neurodevelopmental outcomes (NICE, 2014). Whilst discovery of pregnancy

may occur after the period of greatest teratogenic risk and one may suggest the greatest risk has already occurred, there is a limited evidence base that valproate use in the second and third trimester can be associated with neonatal problems. It is therefore important to encourage minimisation of this risk. To achieve this, The British Association of Psychopharmacology (BAP) suggest withdrawing valproate over the course of four weeks (Goodwin et al., 2016) and introducing an antipsychotic such as olanzapine (McAllister-Williams et al., 2017).

The SIGN guideline highlights that Wisner (2004) failed to find any benefit for sodium valproate and as such places particular emphasis on the merits of using antipsychotics as mood stabilisers. Sharma et al. (2006) illustrated their value in a study, which assessed relapse rate in 25 postnatal women with a history of bipolar disorder. They found that 57.1% of women in the non-olanzapine group relapsed, compared with 18% of those who had taken olanzapine. In addition, a literature review by Epstein et al. (2015) reported no risk of congenital malformations from atypical antipsychotic use in pregnancy.

The importance of clinicians avoiding valproate use is further illustrated by the Medicines and Healthcare products Regulatory Agency (MRHA) publication, the 'valproate toolkit' (2017). This is a guideline for clinicians about the use of valproate and educating women and girls who are currently taking or candidates for the drug. A recent patient safety alert (MRHA, 2017) revealed that in a sample of 624 taking valproate, 20% were not aware of any of the risks of valproate during pregnancy and <20% had received any educational materials.

The BAP guidance (McAllister-Williams et al., 2017) does suggest that in situations whereby a patient has been unresponsive to all other medication, the ban on valproate may not apply. In a situation such as this, the negligence highlighted by the aforementioned patient safety alert becomes particularly relevant. It is imperative that a patient-centred risk-benefit analysis is conducted in a manner that gives the patient autonomy and access to information about valproate and all alternatives, including psychological therapies.

NICE (2014) offers advice regarding selection of an appropriate psychological intervention, advocating the use of structured individual, group and family interventions designed for bipolar disorder to reduce the risk of relapse, particularly when medication is changed or stopped. This type of therapy can therefore be of particular use in those women resistant to recommended mood-stabilisers who do not wish to proceed with valproate.

Alternative options for preventing and managing relapse of bipolar illness in pregnancy and the puerperium.

Thus far, it has been established that the risks of valproate are generally deemed unacceptable. However, in the absence of valproate, alternative measures need to be taken to attenuate the increased risk of relapse during and after pregnancy.

Atypical antipsychotics have been discussed above as a replacement mood stabiliser during pregnancy. However, should a woman decide not to take medication during pregnancy, there is evidence that those with pre-existing bipolar disorder, who start quetiapine or olanzapine on the first day after childbirth, may prevent some but not all early recurrences (Goodwin et al., 2016; McAllister-Williams et al., 2017).

Goodwin et al. (2016) suggest that psychoeducation can help reduce the risk of relapse. As such, it is likely beneficial to inform a woman that stressors, irregular activity patters and poor sleep hygiene increase her risk of an affective illness episode. They also suggest the use of mood diaries. However, the author believes these may be of limited use due to increasing loss of insight as symptoms progress. In place of this, an 'affect tracker' mobile application could be designed where a patient would answer questions several times a day, relating to their affect. Failure to adhere to the agreed schedule or 'red-flag' responses could then be relayed to a key worker who can then follow this up with the patient. This could allow effective monitoring, whilst also providing the patient a less medicalised, more autonomous experience.

In assessing spending on perinatal mental health, Bauer et al. (2014) found that whilst specialist perinatal mental health services are needed for those with complex conditions, only 15% of localities provide these services at full level and more than 40% have no specialist service at all. This likely explains many situations in which valproate is prescribed. However, this is unacceptable and there is a need to challenge the inequity of services across the country. If there was an increase in these services, women could have the specialist support they require and there may be more scope to support women in postponing drug treatment during pregnancy.

Mother and baby units (MBU) could help support this option. The benefits of MBUs have been known for more than 50 years (Main, 1958). A recent study found that mental illness improved markedly in 69% of women: 16% of women with no symptoms at discharge and 53% with marked improvement (Glangeaud-Freudenthal et al., 2011). Furthermore, MBUs have been found to be most effective in helping those with an affective or transient psychotic disorder (87% and 85% improvement respectively), as is the concern with bipolar disorder during pregnancy (Glangeaud-Freudenthal et al., 2011; Bell et al., 1994). If MBU services were increased to allow for more availability to attend in periods of difficulty throughout pregnancy, relapse may be prevented in some cases, in the absence of medication.

It is believed that the lack of social or occupational integration experienced by the, often marginalised, mentally ill may be a risk factor for illness (Glangeaud-Freudenthal et al., 2011). This is particularly relevant in pregnancy when one's physical state may demand more time off work.

The success of the MBU suggests that in the absence of other medication choices, valproate use may not be the best option, as the harmful effects that valproate can have are irreversible. Whilst there is more uncertainty without drug treatment, diligent perinatal community psychiatric teams and MBU facilities could protect the foetus during gestation and then protect mother and child postnatally.

Conclusion:

In order to determine whether the implications of mood stabilisation with valproate during pregnancy are worse than the risk of relapse of illness, the author first explored evidence that shows that pregnancy and the puerperium exacerbate frequency and severity of bipolar illness. Subsequently, a brief review illustrated the wide range and severity of the complications that may arise from gestational valproate use. At this stage, the impression was that valproate carried the greater risk in these two situations. Exploration of national guidance served to raise further concern, showing that valproate is essentially banned and atypical antipsychotics are the current drug of choice.

However, the guidelines do state that valproate use may be acceptable when all other pharmacological interventions have been ineffective. This prompted an exploration of possible non-pharmacological management, which revealed that due to lack of funding and sufficient specialist services across the UK, the potential for MBU and psychological therapies has not been realised.

The scope for these specialist services to reduce the risk of relapse or attenuate the impact should one occur needs to be fully explored in lieu of prescribing such a harmful drug. As such, it is the opinion of the author that the risk of valproate complications does exceed the risk of relapse, particularly when one considers that the teratogenic and neurodevelopmental problems caused by valproate are likely to be life-limiting.

However, since only the mother and her child will subsequently have lived experience of potential complications, a wealth of clinical knowledge is imperative to facilitate a decision that must focus on autonomy and patient-centred care.

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