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Fetal valproate syndrome: a review

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Valproic acid (VPA) is commonly used in the treatment of epilepsy due to its broad range of anticonvulsant activity and relative freedom from side-effects. It is also used in the treatment of bipolar affective disorder. Although, its teratogenic effects are well known, the exact mechanism by which it causes these effects is unclear. This review summarises the range of adverse effects that may be seen in Fetal Valproate Syndrome (FVS), the postulated theories for the mechanism of teratogenesis and guidelines for the management of women with epilepsy.

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Introduction

Valproic acid (VPA) or 2-propyl-pentanoic acid was first introduced for use as an anti-epileptic drug in 1964 and is still a commonly used antiepileptic drug (AED) worldwide, despite the increased awareness of its adverse effects, particularly when taken during pregnancy. It is also used in the treatment of psychiatric illnesses such as bipolar disorders. Approximately one in 250 pregnancies is known to be exposed to anti-epileptic drugs[1] and a significant proportion of these are exposed to valproate, either as mono-therapy or as part of a polytherapy drug regimen. It is a known teratogen and may result in multiple birth defects, dysmorphic facies, developmental delay, learning difficulties and/or behavioural problems. 'Fetal Valproate Syndrome' is the term used to encompass these teratogenic effects.

Sodium valproate is the sodium salt of valproic acid, which is thought to mediate its action by modulating enzymes involved in synthesis and degradation of GABA (gamma amino butyric acid) and sodium channels[2]. In addition, it may also have a direct effect on mitochondria, thereby impairing cellular energy metabolism[3]. It is widely used due to its broad range of anticonvulsant effects. It is also relatively free from sedative side-effects[3] compared to other antiepileptic drugs such as carbamazepine (CBZ) and phenobarbitone. It is 80–90% bound to plasma proteins, is conjugated in the liver and has a short half-life. The dose of VPA is titrated according to the clinical response[3]. VPA crosses the placenta probably by a process of diffusion rather than placental binding[4] and is found in a higher concentration in the fetus compared to the mother[3].

The first report[5] of the adverse effects of valproate was published in 1980. The term 'Fetal Valproate Syndrome' (FVS)[6] was suggested by Di Liberti in 1984, following several other case reports of the teratogenic effects of VPA, all of which documented similar major and minor anomalies. Ardinger summarised the findings of 15 children with FVS in 1988 and pointed out that at least two-thirds of them (10/15) also had neurodevelopmental problems on follow-up[7]. More recently, there has also been a better recognition of the behavioural

phenotype[8,9] in FVS. Although, several retrospective and prospective studies have been conducted to study the risks associated with prenatal exposure to VPA, few have provided conclusive evidence. This is because only few of these studies can be considered 'epidemiological' and have the statistical power to determine specific risk figures[10,11]. A summary of the features of FVS, as documented so far, is described in this review (Table 1).

Pregnancy and neonatal period

There have not been any reports of increased risk of maternal complications during pregnancy, instrumental deliveries or birth asphyxia[3] in FVS. A high incidence of stillbirths[12] and perinatal mortality[13] has been reported in the past, but has not been subsequently reproduced in other studies. The majority of babies are of average birth weight, although 10% may be small for gestational age and about 11–17% may have a large birth weight of over 4 kg[14,15]. Microcephaly (head circumference < 3rd centile) is more frequently associated with other antiepileptic drugs such as CBZ rather than VPA[16].

There is an increased rate of admission to Special Care Baby Units due to withdrawal symptoms and major malformations. Withdrawal symptoms may present as feeding difficulties, hypoglycaemia, jitteriness, irritability and hypothermia and are seen frequently in the early postnatal period[8,17]. The affected babies are often noted to be floppy with poor muscle tone and joint laxity.

Congenital malformations

There is a 6-9% risk of congenital malformations in infants exposed to VPA prenatally, compared to 2-3% in the general population[3,18-21]. Some studies have reported the risk to be even higher, 8–10%[22] and 14%[15] although a recruitment bias cannot be ruled out in these studies. The incidence of congenital anomalies increases when there is exposure to VPA as part of a polytherapy regimen. Kozma[14] reviewed the literature from 1978 to 2000, studying 69 children with FVS and reported that the most frequent malformation was musculoskeletal (62%). Fusion abnormalities such as neural tube defects, cleft palate, hypospadias, trigonocephaly (premature fusion of metopic suture) and rarely, colobomata of the iris have been reported in FVS.

Table 1 Specific features related to FVS

Neural tube defects
Trigonocephaly
Radial ray defects
Pulmonary abnormalities
Coloboma of iris/optic disc
Low verbal IQ
Autism and autistic spectrum disorder

Neural tube defects

There is an increased risk of spina bifida with both VPA (1–2%)[23-27] and CBZ (0.5–1%)[28] exposure compared to the general population risk of 0.2–0.5%[7,29]. VPA is associated with very low lumbar or sacral neural tube defects suggesting that VPA perhaps affects primarily the lowest closure site of the neural tube[3,30]. The ratio of spina bifida to anencephaly with VPA exposure is 33:1 and the majority of these children have hydrocephalus[30]. Several groups[26,27,30] have postulated that neural tube defects following VPA exposure may be dose-related (VPA> 1000 mg/day).

Congenital heart defects

In the study by Kozma[14], 26% of the patients studied had a cardiovascular abnormality with VPA exposure. The most frequently reported lesions in decreasing frequency were ventricular septal defects, aortic stenosis, pulmonary stenosis and patent ductus arteriosus. Two cases with anomalous right pulmonary artery following VPA exposure have been reported[31].

Orofacial clefts

It has been suggested that oral clefts are only seen when VPA is used in combination with other AEDs[29]. Two children with cleft palate after exposure to VPA monotherapy have, however, been reported[3]. Cleft lip, on the other hand, has not been reported with VPA exposure alone.

Limb defects

The risk of a limb abnormality from VPA exposure has been estimated to be about 0.42%[32]. This may include radial ray defects[33-35], split hand[36], postaxial polydactyly[37] and preaxial polydactyly[38]. Reduction malformations of the arms, hypoplastic or absent humerus or radius, ulnar or tibial hypoplasia, absent fingers or oligodactyly, over-riding toes and talipes have all been reported with VPA exposure. Contractures of the small joints of the hands were the most common musculoskeletal manifestation in children with VPA exposure[14].

Genitourinary defects

Hypospadias and undescended testis have been seen more frequently with VPA exposure[39]. Renal abnormalities including renal hypoplasia[33,40], hydronephrosis[41] and duplication of the calyceal system[42] have been reported less frequently.

Craniosynostosis

A prominent metopic ridge (due to premature fusion of the metopic suture) resulting in trigonocephaly (triangular shaped head, as viewed from above) is commonly noted with VPA exposure and may sometimes be severe enough to necessitate surgery. It has been reported that the IQ of the child may be affected if surgical intervention is not offered before the age of 6 months[43].

A variety of other structural anomalies, which are less frequently seen, have also been reported. Table 2 lists the common and rare structural abnormalities seen in FVS. Figures 1 and 2 show some examples of major and minor malformations seen in FVS.

Dysmorphic features

Several groups[3,6,44] have described the features of FVS as consisting of a prominent metopic ridge, thin arched eyebrows with medial deficiency, epicanthic folds, infraorbital grooves, broad nasal bridge, short anteverted nose and a smooth, long philtrum with a thin upper lip. However, it is not the individual dysmorphic features, but the facial gestalt that provides clues to the diagnosis of this condition. These features are best appreciated in infancy as the dysmorphic features become less obvious with age. There has been increasing recognition that the facial gestalt may be a helpful predictor of learning difficulties in those with obvious dysmorphism[15,45]. Figure 3 shows a child with facial features of FVS.

Developmental delay

Global developmental delay is noted only in the severely affected cases. In general, the most frequently affected developmental aspect is speech and language[8,46,47]. There is a delay in both the comprehension and expression of speech and hence early speech therapy should be considered in these children. Those with motor developmental delay may benefit from physiotherapy. Poor muscle tone and poor co-ordination (including poor fine motor skills and hand-eye co-ordination) is frequently seen and interferes with the daily activities of the children, presenting as difficulty in dressing up, poor handwriting, difficulty in riding a bike and swimming. These children are often described as being 'clumsy'. Poor social interaction is also noted with increased frequency in children less than 5 years of age[47] and may correlate with the diagnosis of autistic spectrum disorder in some of these cases. Toilet-training is particularly affected and although most affected individuals do eventually achieve this milestone, some may be in their second decade before they do so.

Table 2 Anomalies associated with valproate exposure

Neural tube defects	Spina bifida Anencephaly
Congenital heart defects	Ventricular septal defect Atrial septal defect Aortic stenosis Patent ductus arteriosus *Anomalous right pulmonary artery*
Limb defects	Radial ray defect Polydactyly Split hand Overlapping toes Camptodactyly *Ulnar or tibial hypoplasia* *Absent fingers* *Oligodactyly*
Genitourinary defects	Hypospadias *Renal hypoplasia* *Hydronephrosis* *Duplication of the calyceal system*
Brain anomalies	*Hydranencephaly* *Porencephaly* *Arachnoid cysts* *Cerebral atrophy* *Partial agenesis of corpus callosum* *Agenesis of septum pellucidum* *Lissencephaly of medial sides of occipital lobes* *Dandy-Walker anomaly*
Eye anomalies	*Bilateral congenital cataract* *Optic nerve hypoplasia* *Tear duct anomalies* *Microphthalmia* *Bilateral iris defects* *Corneal opacities*
Respiratory tract anomalies	*Tracheomalacia* *Lung hypoplasia* *Severe laryngeal hypoplasia* *Abnormal lobulation of the right lung* *Right oligaemic lung*
Abdominal wall defects	*Omphalocoele*
Skin abnormalities	Capillary haemangioma *Aplasia cutis congenita of scalp*

*Rare structural abnormalities are shown in italics

Childhood medical problems

Visual problems such as myopia and strabismus are noted with increased frequency. The myopia may present relatively early in these children. Hearing problems due to recurrent otitis media with effusion is common[8,46]. Joint laxity and flat feet, affecting the gait of the individuals is seen. Generalised joint laxity has been reported in up to 70% of children exposed to VPA[8,46].

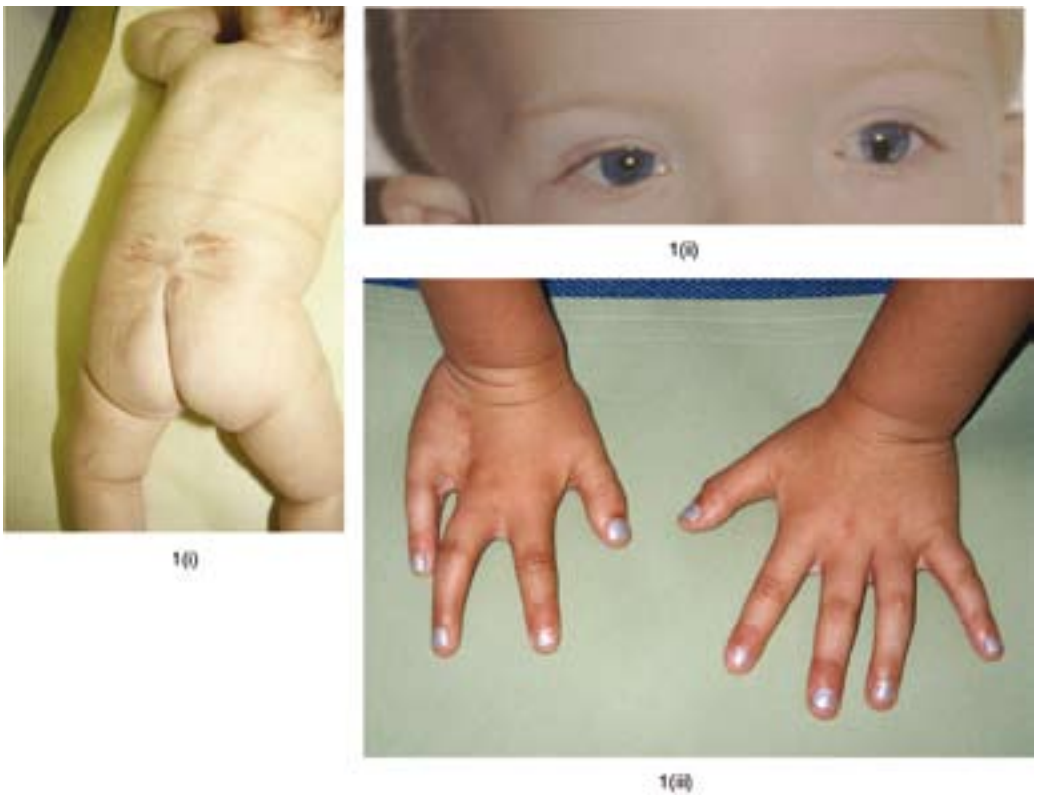

Figure 1 Examples of major malformations seen in FVS. (i) Repaired neural tube in lumbo-sacral region (ii) Coloboma of the iris (iii) Split hand.

Learning difficulties

The average full-scale IQ of a child affected with FVS is in the 80-90 range[47]. However, the verbal IQ of these individuals is significantly lower[47] and appears to be the continuum of the speech problems noted in early childhood. In severely affected individuals, the IQ may fall into the 30–40 range. Hence, mild to moderate mental retardation is more common in FVS than severe mental retardation and only a minority of patients are likely to require supervision as adults.

A large proportion of the children need extra help at school and some of them may be in need of one to one help. In one study, 40% of children with VPA exposure were on an additional educational needs register and 30% were statemented (requiring one to one help)[47]. These figures may, however, reflect the self-selection bias of the

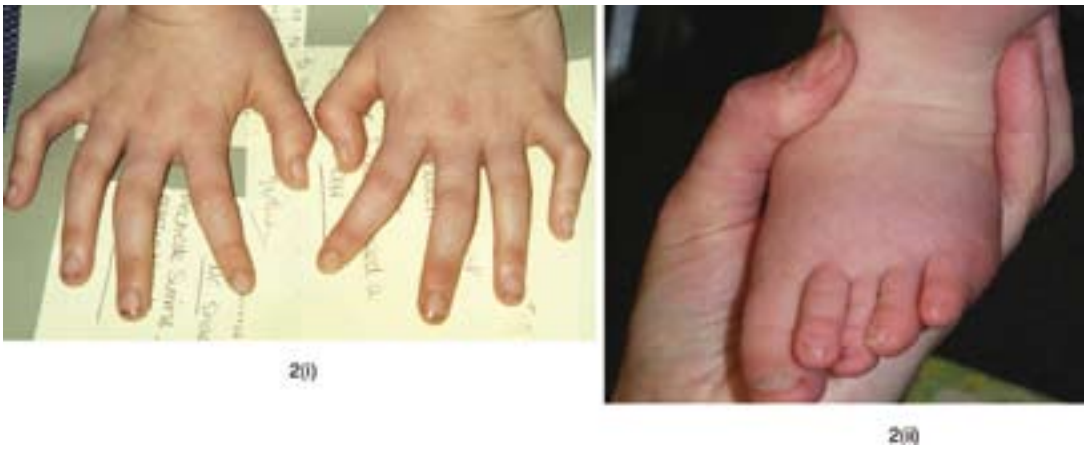

Figure 2 Examples of minor malformations seen in FVS. (i) Fixed flexion contracture of fingers (ii) Overlapping toes.

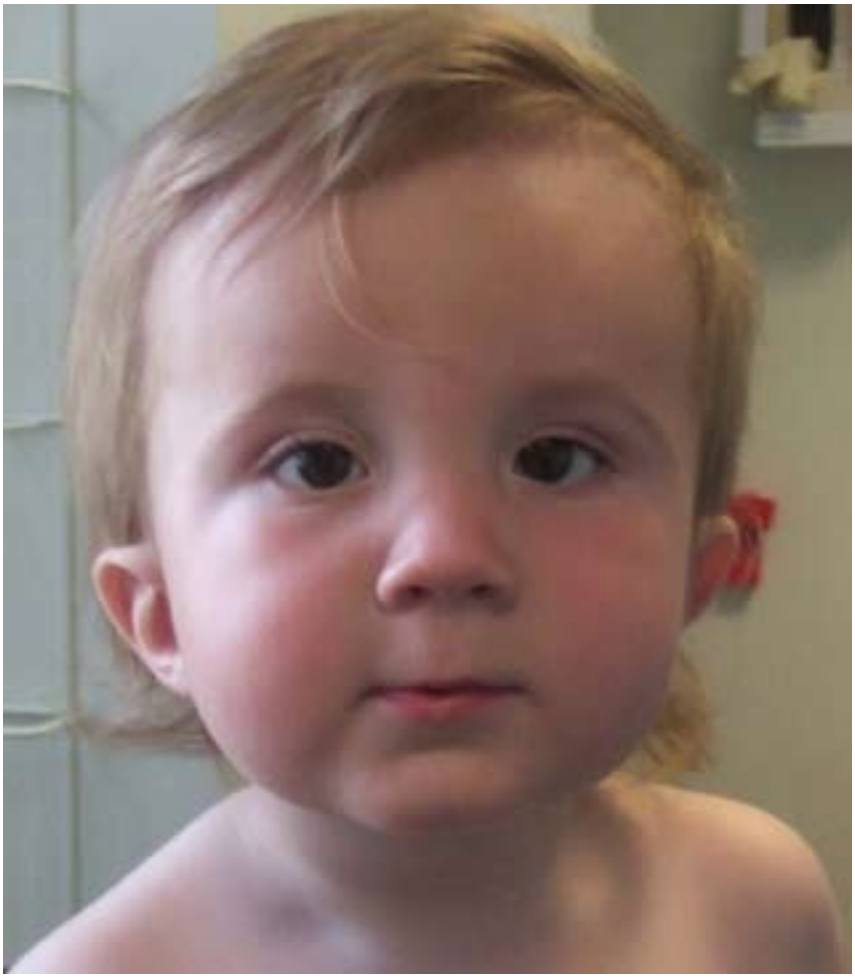

Figure 3 Child with facial features of FVS: trigonocephaly which has been surgically repaired, broad forehead, thin arched eyebrows, flat nasal bridge, infraorbital grooves, short anteverted nose, long and smooth philtrum and thin upper lip.

participants in the study, as only 40% of those that were approached agreed to take part[47].

Behavioural problems

Autism, Asperger's syndrome and autistic spectrum disorder have been diagnosed and reported more frequently in FVS[8,46]. Disruption of early embryonal serotonergic neuronal development has been implicated in the aetiology of the autism in FVS[48]. Poor concentration and hyperactivity have also been commonly reported. Immature behaviour with inappropriate affection towards strangers is often seen in the most severely affected cases. Table 2 summarises the malformations associated with VPA exposure.

Mechanism of teratogenicity

The exact mode of action of the drug by which it causes the teratogenicity is unknown. Pharmacological studies indicate that the anticonvulsant activity is less likely to be mediated by the same target as the teratogenic effects[2]. It has been hypothesised that a gene-environment effect may be responsible for the adverse effects in utero, as there is an increased recurrence risk of FVS in siblings, if the medication and its dose remain unchanged in the mother during a subsequent pregnancy[8,46,49]. In the past, the genetic factor was thought to be in the form of epoxide hydrolase, an enzyme involved in VPA metabolism, the inhibition of which results in accumulation of epoxides, a possible teratogen[12,50]. Other factors linking the metabolism of VPA and its teratogenicity are alteration in intracellular pH[26,51], interference with embryonic lipid metabolism[52] and zinc metabolism[24,53,54].

Animal studies with mice have suggested that altered expression of specific HOX genes may account for some of the malformations in VPA-exposed fetuses[55]. Folic acid deficiency in pregnant women on antiepileptic medication, exaggerated by the co-existence of reduced activity of the methylenetetrahydrofolate reductase (MTHFR) enzyme, caused by a common polymorphism C677T in the MTHFR gene, has been implicated as

a causal factor in the teratogenicity[56]. A differential expression of the folate binding protein (FBP-1) has been demonstrated between VPA sensitive and VPA resistant mice[57]. The same group also demonstrated significantly higher MTHFR gene expression levels throughout the period of murine neural tube closure in the VPA resistant mice and suggested hypomethylation, which alters essential gene expressions during critical periods of neural tube closure, as the cause of the teratogenicity in the VPA-sensitive mice[57]. More recently, it has been shown that VPA analogues that are inhibitors of Histone deacetylase (HDAC) cause similar developmental defects as other structurally unrelated HDAC inhibitors (e.g. Trichostatin A) in both Xenopus and zebrafish[2]. HDACs regulate chromatin structure and hence gene expression. HDAC inhibition leads to the transcription of only certain genes, which are often genes associated with cessation of cell proliferation or apoptosis.

Discussion

FVS is relatively easy to diagnose when a patient presents with all of the above features together with a clear-cut history of maternal valproate ingestion. This is, however, often not the case. Also, there is a wide variation in the clinical presentation of the condition, even between siblings, thereby adding to the diagnostic difficulty. The most difficult cases to diagnose are the ones where the learning and behavioural problems present later on in life, in the absence of specific physical abnormalities. This variability in clinical presentation may be influenced by a number of factors such as maternal seizures during pregnancy, folic acid intake, dose and timing of exposure of VPA, parental factors such as IQ and socio-economic status and genetic susceptibility. A diagnosis of 'fetal valproate effects' should be considered when a child with a history of VPA exposure in utero presents with features suggestive but not conclusive of the diagnosis of FVS[15].

VPA-specific effects such as trigonocephaly, radial ray defects and neural tube defects may indicate the diagnosis more easily. Neural tube defects have been reported with exposure to other AEDs such as CBZ and lamotrigine[21], but not as frequently. Pulmonary abnormalities such as oligaemic lung or abnormal lobation of the lung and ophthalmic abnormalities such as colobomata of the iris have not been reported with any other antiepileptic drug exposure, but only present themselves occasionally even with VPA exposure. Rib abnormalities have been frequently reported in mice with VPA exposure[55,58] but there have been no such reports in humans. This may be due to the fact that chest radiographs are not routinely performed as an investigative procedure in the diagnosis of FVS. A significant decrease in verbal IQ has been reported with VPA but not with other antiepileptic drugs. Although autism and autistic spectrum disorder have not been reported with exposure to any other antiepileptic drug than VPA, idiopathic autism is relatively common in the general population and without additional features is not discriminatory in the diagnosis of FVS.

The timing of exposure and the dose of the drug are important in influencing the outcome of pregnancy. First trimester exposures are more likely to result in malformations as this is the main period of structural development in the fetus[59]. The risk of cognitive and behavioural impairment may be increased by VPA exposure throughout the pregnancy, as the fetal brain continues to grow up to about two years of age. Specific dose-related features described with VPA exposure are neural tube defects, obviously dysmorphic face and a reduction in verbal IQ. There is accumulating evidence that radial ray defects may also be dose-related. In general, a dose of > 1000 mg/day has been implicated for all of these abnormalities.

FVS is a diagnosis of exclusion. Other fetal insults such as alcohol, toluene and diabetes may mimic some of the features of FVS. Specific malformations such as trigonocephaly and radial ray defects are also features of other dysmorphic syndromes, which may need to be ruled out before assigning a diagnosis of FVS. This is important because the diagnosis will impact upon the recurrence risk quoted for future pregnancies.

The efficacy of VPA as an AED cannot be disputed, but the extent of its teratogenic effects cannot be under-estimated either. Hence, the balance between the therapeutic effects of this drug and its teratogenic effects is critical in the management of women with epilepsy, particularly in those with idiopathic generalised epilepsy[60]. In localisation-related epilepsy, alternatives such as CBZ are effective and should be used due to their relative safety during pregnancy. It is known that VPA at a dose of >1000 mg/day may be associated with an increased risk of both malformations and learning difficulties. It is therefore advisable for women taking VPA to reduce the dose to <1000 mg/day, if possible. This should be done in liaison with their clinician and well in advance of the pregnancy, as the effect of seizures during pregnancy can be detrimental to the health of the mother and child alike. Also, women who take more than one medication for control of their epilepsy should be advised to change to monotherapy if possible, as polytherapy is reported to be more harmful[61]. It is prudent to start tailoring the medication from the early teenage years in young girls with epilepsy or psychiatric illness.

High dose folic acid (4 mg/day) is recommended during pregnancy[61], starting at least 6 weeks pre-conception and continuing through the first trimester. Folic acid supplements are thought to be protective against malformations, in particular against neural tube defects. Some clinicians are of the opinion that it may be advisable for these women to continue the folic acid until delivery, due to the continued development of the fetal brain throughout the pregnancy. Serum alpha-feto-protein levels in the second trimester may be helpful in picking up open neural tube defects. Antenatal scans should be able to pick up most major malformations, especially if specific attention is being paid towards anomalies known to be associated with FVS. Some anomalies such as anencephaly may be picked up as early as late first trimester, whilst others such as isolated cleft palates may be difficult to identify altogether. However, scans during pregnancy are unable to predict future learning disabilities unless obvious structural brain abnormalities are seen.

None of the AEDs available currently are completely safe during pregnancy, but VPA appears to be the most teratogenic of them all[8,21,45,46,47]. Large population-based prospective follow-up studies are currently underway, the results of which may give us further conclusive evidence regarding the scale and intensity of the teratogenic effects of valproate.

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