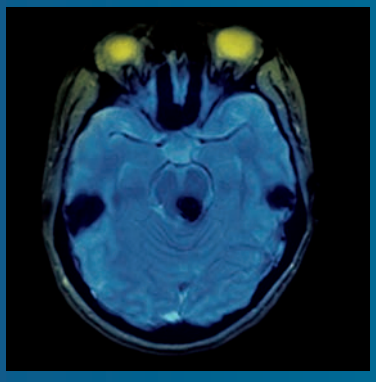
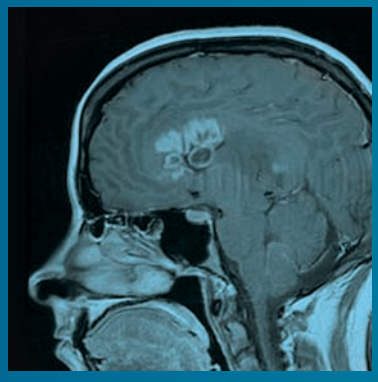
SERIES IN
MATERNAL-FETAL
MEDICINE

Neurology and Pregnancy

Clinical Management





Edited by

Michael S Marsh
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Neurology and Pregnancy

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Foreword

This volume is most timely. If non-neurologists approach our specialty with trepidation, most neurologists and neurosurgeons confront obstetrics and its many neurological aspects with equal uncertainty. The reasons are obvious. In pregnancy we are dealing not with a single patient, but with a woman, her unborn (or newborn) child, and a complex web of relationships surrounding them.

Thus a text that provides an assessment that is clear, scholarly, yet common sense and evidence-based (where evidence exists), of the interactions between science and clinical practice across the spectrum of neurological and neurosurgical challenges in pregnancy, is sure to find a wide and grateful readership. The editors have succeeded in welding into a coherent and authoritative whole a somewhat fragmented but vitally important and rapidly evolving field of clinical science.

Neurologists who work in a general hospital setting will wish to have this text to hand, as will obstetricians. All those who train neurologists and obstetricians will wish to ensure that this volume is readily available to their trainees. In practical terms, this enterprise will surely help to improve the care of people in whom pregnancy is complicated by neurological problems and the care of those with pre-existing neurological disorders who become pregnant. All these individuals and families require advice and care supported by sound evidence to ensure a safe and happy pregnancy, delivery and post-natal period. Towards this goal, *Neurology and Pregnancy* represents a landmark in clinical neurosciences and in obstetrics.

Nigel Leigh
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Foreword

Neurological disease in pregnancy is now the second commonest cause of maternal death in the United Kingdom. Many of the pregnant or puerperal women who have died from epilepsy, subarachnoid haemorrhage and other neurological disease have done so without the benefit of pre-pregnancy counseling, appropriate multidisciplinary care, or timely involvement of neurologists. Therefore the development of a specific text addressing the issues of management of neurological disease in pregnancy is timely.

This authoritative reference brings together experts in the field of neurology, fetal medicine, obstetrics, genetics and psychiatry. The general chapters cover important issues such as pharmacokinetics of drugs in pregnancy and breastfeeding and neuroimaging, an understanding of which is a prerequisite to optimising management of pregnant women with neurological problems.

Part II covers pre-existing as well as new-onset neurological disease presenting in pregnancy, and includes chapters on common clinical problems such as blackouts, headaches and epilepsy, as well as dealing with less common problems such as peripheral nerve disease, myasthenia and stroke, which are also comprehensively covered.

Many of the chapters are the result of multidisciplinary collaboration reflecting the teamwork that should accompany optimal management of neurological disease in pregnancy. This book will provide a useful reference for all those who manage women of childbearing age with neurological disease as well as for obstetric care providers faced with common and less common neurological conditions complicating pregnancy.

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Preface

Dear Colleague

The management of neurological disorders in pregnancy is based on a good knowledge of the woman's medical and social history, available evidence and previous pregnancy outcomes, as well as an appreciation of her attitudes, beliefs, concerns and priorities. It calls for knowledge, judgement and experience and is as much an art as it is a science. It often requires balancing conflicting interests and supporting the patient and her partner in making potentially far-reaching decisions, sometimes based on insufficient evidence. It requires sharing the decision making process, aimed at ensuring the best outcome for both mother and child, so that the woman does not feel she alone carries the burden.

Advising a pregnant woman with a neurological presentation is by its nature a multidisciplinary process. No one specialist can do this alone and it is only by combining our skills and knowledge that we can provide the best care. This truly multidisciplinary book provides much of the background knowledge-base needed, both within and across specialties. Few volumes cover its scope. Moreover, where evidence is limited, authors have not shied away from giving sound clinical guidance.

We are enormously grateful to our contributing authors for generously sharing their expertise and for our publisher's patience in what has been a longer gestation than first envisaged. Our hope is that you, our reader, will explore sections in your field as well as other disciplines, and in doing so value this volume and learn from it as much as we have.

Michael S. Marsh
Lina A. M. Nashef
Peter A. Brex

Editorial Note on the FDA Classification of Drugs and Pregnancy

Many of the following chapters refer to the US FDA pregnancy category ratings for the teratogenicity of a drug, which are currently set out as follows:

Category A
Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy, and there is no evidence of risk in later trimesters.

Category B
Animal reproduction studies have failed to demonstrate a risk to the fetus, but there are no adequate and well-controlled studies in pregnant women.

Category C
Animal reproduction studies have shown an adverse effect on the fetus: there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Category D
There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Category X
Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience; the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

However, this classification has been proposed for review as some feel it is potentially misleading, and the reader is therefore advised to consult their pharmacists for the latest safety information when considering the use of a drug during pregnancy or during breastfeeding.

Contents

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Neurogenetics and pregnancy

Dragana J. Josifova

INTRODUCTION

Neurogenetics has been one of the most intensively researched areas in medicine over the last few decades, a time which has seen an exponential growth in our knowledge of the molecular basis of health and diseases. A number of genes associated with neurological disorders have been identified and we are beginning to understand the complex network of molecular pathways involved in the development, function and maintenance of the nervous system. Diagnostically useful genetic tests for some paediatric and adult-onset neurological disorders have become readily available. Pre-symptomatic and prenatal tests can now be offered and, for some conditions, pre-implantation genetic diagnosis has become possible. This chapter outlines basic principles as well as many illustrative examples.

Genetic Code

There are approximately 25,000 genes in the nucleus of a human cell. Each gene is represented by a unique DNA code. Individual genes are strung by repetitive DNA sequences into condensed stretches of DNA called chromosomes. There are 46 chromosomes in the human genome arranged in 23 pairs, with one member of the pair coming from each parent (Fig. 1.1). One set of 23 chromosomes constitutes the haploid number; the normal chromosome complement is diploid.

The first 22 pairs are autosomal chromosomes (numbered from 1 to 22) and the 23rd pair comprises the sex chromosomes, X and Y. Males are hemizygous for the genes on the X chromosome (they have only one copy of these genes). In females, one of the X chromosomes is randomly inactivated to preclude over expression. Each chromosome carries hundreds of genes. The genes, like chromosomes, come in pairs with the exception of the genes on the X and Y chromosomes in males. Males inherit their X chromosome genes from their mothers and their Y chromosome genes from their fathers.

CHROMOSOME REARRANGEMENTS

The normal chromosome complement may be altered in number or individual chromosome structure. Regardless of the mechanism, a chromosome rearrangement may lead to a gain or loss of genetic material. This is frequently associated with phenotypic consequences: from mild learning difficulties to a complex picture including restricted intrauterine and postnatal growth, unusual physical features (dysmorphic features), structural abnormalities of organs and systems, epilepsy and significant disability. Pregnancies affected with chromosomal abnormalities are at increased risk of miscarriage.

1. *Rearrangements affecting chromosome number*
   a. *Aneuploidy*
      Aneuploidy means that the chromosome complement does not equal a multiple of the haploid number of chromosomes. Common aneuploidies are the trisomies: Down syndrome (trisomy 21), Patau syndrome (trisomy 13), Edward syndrome (trisomy 18). Aneuploidies involving other autosomal chromosomes are not viable and usually result in early miscarriage. Aneuploidies involving the sex chromosomes are relatively common. With the exception of Turner syndrome (45,X), they are not associated with early pre- and post-natal recognisable phenotype.
   b. *Polyploidy*
      Polyploidy implies that there are more than two full haploid sets of chromosomes, for example, triploidy (69 chromosomes) or tertraploidy (92 chromosomes). These are usually associated with early miscarriage; however, live birth is possible if the polyploidy is in a mosaic pattern with a cell line which has a normal chromosome complement.
2. *Structural chromosome rearrangements*
   a. *Chromosome translocations, deletions and duplications*
      When portions of two or more chromosomes exchange places, but the total amount of genetic material remained unchanged, the rearrangement is called a balanced translocation (Fig. 1.2). About 1 in 500 healthy individuals carries a balanced chromosome rearrangement. Carriers of balanced chromosome rearrangements, although healthy, are at risk of passing the rearrangement on to their offspring in an unbalanced fashion. Unbalanced chromosome rearrangements are characterised by a deficit or excess of genetic material. Pregnancies affected with structural chromosome rearrangements have an increased risk of miscarriage.

      If both parents have normal chromosomes, a chromosome rearrangement identified in their offspring is considered to be de novo. The risk of recurrence of a de novo rearrangement in future pregnancies is low, approximately 1%, due to the possibility of germline mosaicism.

      Germline mosaicism means coexistence of gametes with normal and abnormal chromosome complement or normal and mutated single gene. Somatic mosaicism, however, concerns tissues other than the reproductive ones. Both, germline and somatic mosaicism arise as a result of a post-zygotic event. Somatic mosaicism may sometimes be identified in the DNA extracted from peripheral lymphocytes, but it is more likely to be found in chromosomes/DNA from solid tissue, for example, skin.

      If one parent carries a balanced translocation, the risk of miscarriage and the risk of having a child with unbalanced chromosome rearrangement vary depending on the nature of the rearrangement. De novo, apparently balanced translocations identified at prenatal diagnosis (PND) carry a risk of abnormalities up

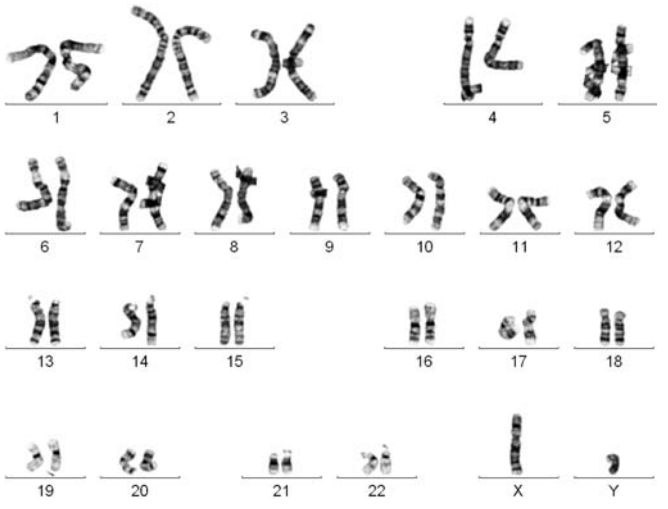

Figure 1.1 Normal male chromosome complement.

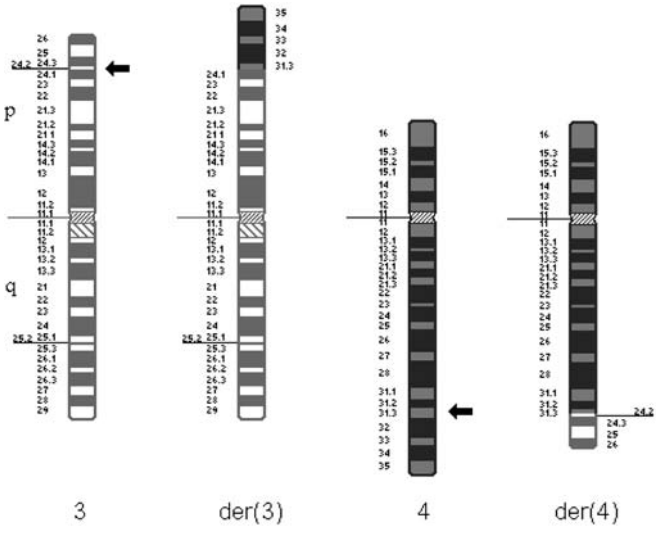

Figure 1.2 Balanced translocation between chromosomes 3 and 4.

to 10%, because of cryptic deletions/duplications at the break points or disruption of important genes.

b. *Robertsonian translocation*
Robertsonian chromosome translocations (RTs) involve only the acrocentric chromosomes: 13, 14, 15, 21 and 22. Acrocentric chromosomes have very small short (p) arm, coding DNA. The RT arises when two acrocentric chromosomes fuse at the centromere, each having lost their short (p) arm, to form a recombinant chromosome made up of the long arms of the chromosomes involved in the translocation (Fig. 1.3). The diploid number is therefore reduced by one chromosome and equals 45. As no coding DNA has been lost or gained, the carriers of RT do not exhibit any abnormalities. However, these translocations usually have reproductive implications. RTs often lead to chromosome imbalance in the offspring and predispose to early miscarriage. Males with RTs may have reduced fertility.

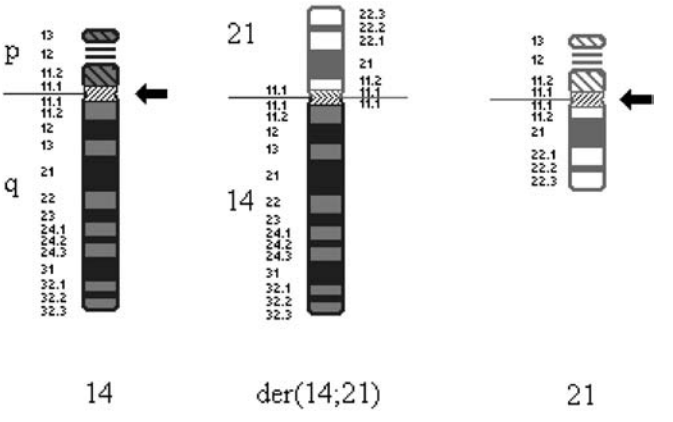

Figure 1.3 Balanced Robertsonian translocation between chromosomes 14 and 21.

SINGLE GENE DISORDERS

The DNA sequence of a gene is a template for protein synthesis. A change in the DNA sequence (mutation) alters the template and interferes with protein synthesis. Depending on the nature of the mutation, protein synthesis may be completely abolished or a structurally or functionally abnormal protein may be produced.

Patterns of Inheritance

1. *Autosomal dominant* (AD) conditions are caused by an alteration in only one of the two copies of a particular gene. The offspring of an individual who carries a mutation in only one copy of a gene have a 50% chance of inheriting either the altered or the healthy gene. The inheritance of AD conditions is independent of the gender of either the parent or the offspring.

   AD genes have two important characteristics:

   a. *Variable expression*. This implies that the severity of phenotype between and within families may vary considerably. For example, the age at which individuals who carry mutations in the spastin gene, associated with AD spastic paraplegia, become symptomatic is highly variable, from childhood to well into adult life.
   b. *Variable penetrance* refers to the likelihood of any phenotypic features manifesting in those who carry a pathogenic mutation. For example, the Huntington disease gene is fully penetrant: all individuals who carry the mutation will develop the condition although the age of onset may vary. However, the breast/ovarian cancer predisposing genes (*BRCA1* and *BRCA2*) have reduced penetrance, as not all mutation carriers develop cancer in their lifetime.

A de novo gene mutation occurring in a gamete (sperm or egg) will affect all the cells of the embryo. Conditions like tuberous sclerosis and neurofibromatosis 1 and 2 have a high new mutation rate; therefore, a significant proportion of patients do not have a relevant family history. A new mutation may

Table 1.1 Risk Assessment in Autosomal Recessive Disorders

At conception		
Phenotype	Genotype	Risk
Affected	aa	1 in 4
Carrier	Aa	1 in 2
Not carrier	AA	1 in 4

Abbreviations: A, normal allele; a, allele carrying mutation.

also arise in an embryo as a post-zygotic event. When this occurs, the mutation will be present in some, but not all, cells. This is known as somatic mosaicism and usually gives rise to a milder form of the condition. The severity of phenotype depends on both the percentage and distribution of cells carrying the mutation. The level of mosaicism may vary in different tissues. A genetic test on blood lymphocytes does not necessarily identify or reflect the level of mosaicism in other tissues (e.g., skin or brain tissue) and may not be an accurate predictor of the phenotype.

2. *Autosomal recessive* (AR) conditions arise when both copies of a gene carry a pathogenic mutation. Both parents of individuals affected by AR conditions are almost always carriers. The presence of the same mutation on both copies of the gene is referred to as homozygosity and is more likely to be seen in consanguineous families. Two different mutations in the same gene imply double or compound heterozygosity.

   If both parents are carriers of a mutation in the same, AR gene, then, at conception, there is a 1 in 4 chance of both passing on faulty copies of the gene and having an affected child regardless of the child's sex. There is a 1 in 4 chance of the embryo inheriting two normal copies of the gene and a 50% chance of inheriting only one abnormal copy of the gene conferring a carrier status similar in both parents (Table 1.1).

   There is an increasing recognition of conditions caused by mutations in two different genes (digenic inheritance), which may, although not necessarily, be in the same pathway. For example, holoprosencephaly (a developmental abnormality associated with incomplete separation of the forebrain into two hemispheres) can be caused by simultaneous mutations in both the Sonic Hedgehog (*SHH*) gene (Sonic Hedgehog pathway) and *TGIF* gene (Nodal pathway) (see page 5).

3. *X-linked disorders* result from mutations in genes on the X chromosome. According to the traditional Mendelian teaching, they cause disease in males (X-linked recessive) because of their hemizygous state (having only one copy of X chromosome genes). Female carriers should remain symptom free because of the compensatory effect of the functional copy of the gene on their second X chromosome. X-linked dominant conditions, by contrast, present in females and males, and may be lethal for male embryos (Rett syndrome, Incontinentia pigmenti, Aicardi syndrome).

   However, it is well recognised that females may be manifesting carriers of X-linked recessive disorders and exhibit a wide variety of phenotypic features, from very mild to virtually the full clinical spectrum as seen in affected males (Duchenne/Becker muscular dystrophy). One of the explanations for this is non-random (skewed) X-inactivation. However, X-linked dominant conditions associated with lethality in male fetuses have been seen in male newborn babies, albeit rarely. Affected boys usually have severe phenotype and prolonged survival is rare. For example, Rett syndrome in boys is associated with severe neonatal encephalopathy, unlike in females who, following a period of relative normality in infancy, present with global developmental delay, microcephaly and characteristic behavioural phenotype.

   Therefore, the distinction between X-linked recessive and X-linked dominant disorders is not as strict, which is why the term X-linked disorders (genes) is more commonly used.

   Carrier females of X-linked conditions have a 1 in 2 chance of passing the gene onto their sons and 1 in 2 chance of having carrier girls. At conception, therefore, there is a 25% chance of having an affected offspring.

4. *Mitochondrial disorders* arise by mutations in the mitochondrial DNA (mtDNA) which is exclusively inherited from the mother. MtDNA is different from nuclear DNA and contains only about 30 genes. There are several copies of mtDNA in each mitochondrion and a number of mitochondria in each cell. A mutation may be present in some but not necessarily all mtDNA copies. The combination of normal and mitochondria carrying a mutation is known as heteroplasmy. The ratio between the altered and normal mtDNA determines the mutation load. The severity of phenotype correlates with the mutation load although it is likely that other, modifying genes in conjunction with the environment also contribute to the phenotypic diversity of the disorders caused by mutated mtDNA.

   A large number of nuclear genes regulate mitochondrial function and maintenance. These are transmitted in an AR or AD fashion. Consequently, the majority of mitochondrial disorders are caused by mutations in the nuclear genome, and may carry a 25% or 50% recurrence risk, respectively, in every pregnancy.

FAMILY HISTORY OF NEUROLOGICAL DISORDER

Epilepsy

Epilepsy is the most common neurological disorder requiring long-term and sometimes lifelong treatment. In one study, it was reported to affect 4/1000 people in the United Kingdom (1). The prevalence among women of childbearing age is estimated to be between 6.9 and 7.8 per 1000 (2). Aetiologically this is a very heterogeneous group; a proportion of cases are genetic.

The risk to any child of a mother with epilepsy is related to any potential genetic cause to maternal epilepsy and the effect of the intrauterine exposure to anti-epileptic drugs (AEDs).

Monogenic, AD epilepsy syndromes, for example, *SCN1A*-related Dravet syndrome, in either parent will incur a 50% risk of gene transmission; however, the degree of severity may be very variable. Epilepsy caused by mutations in an X-linked gene, for instance, *FLNA*-related periventricular nodular heterotopia (PNH)_ in the mother, will incur a 50% risk of transmission, with significantly reduced viability of male fetuses; hence the risk of epilepsy would apply largely to the daughters of a carrier mother. By contrast, *PDH19* gene is a gene on the X chromosome, mutations in which cause epilepsy in females; carrier males usually do not develop a seizure disorder, but are at increased risk of psychiatric illness.

It is recommendable that a potential genetic diagnosis is explored and the risk of epilepsy and teratogenic effects of AEDs or fetal anti-convulsant syndrome (FACS) are

discussed prior to conception. If a disease-causing mutation is known, PND or pre-implantation genetic diagnosis may be available. Prospective parents should be given the opportunity to discuss these issues with a clinical geneticist to enable them to make an informed choice.

Fetal Anti-convulsant Syndrome

FACS refers to the teratogenic effects, including congenital malformations, dysmorphic facial features and developmental and behavioural difficulties, in children prenatally exposed to AEDs (3). This is also discussed in chapter 12.

Approximately 1 in 250 pregnancies is exposed to sodium valproate, carbamazepine, phenytoin, lamotrigine or a combination of AEDs. Studies have consistently shown a two- to three fold. Increase in the incidence of congenital anomalies (Table 1.2) in fetuses exposed to AEDs compared to a non-exposed group (Table 1.3). The highest incidence is associated with sodium valproate exposure and polytherapy, and the lowest with carbamazepine monotherapy (4,5). A dose-related effect has been seen with sodium valproate, with another study suggesting a dose-related effect with lamotrigine (chapter 12).

The highest prevalence of facial dysmorphic features (Table 1.4) is seen in the sodium valproate monotherapy group with a significant positive correlation between the severity of facial dysmorphic features and verbal IQ (4).

Table 1.2 Congenital Anomalies Associated with FACS

Major congenital malformations in FACS in order of frequency
Cardiovascular
Musculoskeletal
Cleft lip and/or palate
Neural tube defect
Structural brain malformations
Exomphalos
Reduction limb defects

Abbreviation: FACS, fetal anti-convulsant syndrome.

Table 1.3 Incidence of Major Congenital Anomalies in Pregnancies Exposed to AEDs in Selected Studies

	Kini et al., 2006 (4)	Meador et al., 2008 (5)
All births	6%	7.08%
Monotherapy, overall	–	5.30%
Carbamazepine	5%	5%
Sodium valproate	14%	17.64%
Polytherapy	5%	9.84%

Abbreviation: AEDs, anti-epileptic drugs.

Table 1.4 Dysmorphic Features in FACS

Facial features in FACS
• Bi-temporal narrowing
• Metopic ridge
• Upslanting palpebral fissures
• Hypertelorism
• Epicanthic folds
• Flat nasal bridge
• Infra-orbital creases
• Mid-facial flattening
• Long, poorly formed philtrum
• Thin upper lip

Abbreviation: FACS, fetal anti-convulsant syndrome.

The risk of long-term effect of antenatal exposure to AEDs on development, learning and behaviour has been controversial and difficult to establish due to ascertainment bias, inconsistent assessment strategies and length of follow-up. A 24% overall incidence of learning difficulties in the prenatally exposed children compared to 11% in non-exposed siblings was reported by Dean et al. (3); however, when only the children from families without history of learning difficulties were assessed, 19% of those exposed to AEDs presented with cognitive impairment compared to 3% of their non-exposed siblings (3). These figures are considerably higher than demonstrated in the more recent studies (4,5). After adjustment for maternal IQ, maternal age, AED dose, gestational age at birth and maternal preconception use of folate, at the age of 3 years the children exposed to valproate had an IQ score 9 points lower than the score of those exposed to lamotrigine, 7 points lower than the score of those exposed to phenytoin and 6 points lower than the score of the children exposed to carbamazepine (6) highlighting the highest risk of cognitive function impairment in children prenatally exposed to valproate in a dose-dependent fashion.

The prevalence of combined autistic spectrum and autistic disorder of 1.9% and 4.6%, respectively, in children exposed in utero to AEDs (7) is higher compared to 0.25% in a population-based survey in the United Kingdom using DSM-IV clinical criteria (8).

Confounding factors, including parental IQ, family history of learning and/or behavioural difficulties, autism or speech delay, may influence the neurodevelopmental pattern independently or concomitantly with the potential effects of prenatal AEDs exposure. In this context it is important to consider the possibility of a genetic aetiology of epilepsy in the mother who could present with variable phenotype including cognitive impairment.

The diagnosis of FACS is usually made by the clinical geneticists based on the maternal medical history, child's physical features and developmental pattern.

Preconception counselling should be offered to women of childbearing age to enable them to understand the risks of FACS and make an informed decision. Monotherapy and use of drugs with less teratogenic potential should be considered. However, the majority of epileptic mothers will give birth to a healthy child and the risk of FACS should be balanced against the risk associated with poor seizure control in pregnancy.

Tuberous Sclerosis Complex

Tuberous sclerosis complex (TSC) is an AD, multi-system disorder. The diagnosis is usually clinical and based on major and minor disease criteria (9). About 70% of affected individuals have seizures and a significant proportion have some degree of learning difficulties, behavioural problems and increased susceptibility to psychiatric illness. TSC causes a reduced life expectancy primarily because of CNS tumours and renal disease.

Nearly 60% of affected fetuses develop a cardiac rhabdomyoma. These are rarely seen before the third trimester and are therefore not helpful for early PND. They have a good prognosis and spontaneously resolve in the first few years of life. Active management is only required if they cause outflow obstruction, but if this is not the case at birth, it is highly unlikely that it will develop later.

Post-natally, the diagnosis is made on clinical grounds. As the features evolve over time the findings may not necessarily meet the diagnostic criteria early on and molecular

Table 1.5 Expansion Mutation in MD and Associated Phenotype

Allele size	Phenotype
5–34 (normal)	Healthy
35–49 (permutation)	Unaffected
50–100	Mild phenotype
100–1000 (expansion)	Classical MD
>2000 (expansion)	Congenital MD

Abbreviation: MD, myotonic dystrophy.

analysis may occasionally be undertaken to confirm the diagnosis.

The condition is caused by mutations in one of the two genes: *TSC1* and *TSC2*. Nearly two-thirds of cases represent a new mutation. The gene is considered fully penetrant, although the severity is highly variable within and between families. In some cases, a parent was diagnosed as having TSC only after a diagnosis was made in their child. The extent of clinical features is not a precise predictor of the disease severity, especially not in regard to the epilepsy and cognitive/behavioural phenotype.

The risk to a sibling of a singleton case is approximately 1%, assuming that the parents do not manifest any features of TSC on careful clinical examination by a trained professional, and that their ophthalmological examination and renal ultrasound scan are normal. The residual risk is due to germline mosaicism.

Molecular analysis of *TSC1* and *TSC2* genes identifies mutations in approximately 60% of clinically diagnosed cases. PND by gene testing is available if the disease-causing mutation in the proband has been confirmed. It is however not possible to predict the severity of the condition.

Myotonic Dystrophy

Myotonic dystrophy (MD) is an AD, multi-system disorder caused by a CTG triplet repeat expansion in the *DMPK* gene. The age of onset and disease severity correlate to some degree with the size of the expanded allele.

The expanded allele is unstable and tends to expand further when it is passed from one generation to the next (genomic anticipation) (Table 1.5). This phenomenon occurs more commonly in female meiosis. Congenital MD (caused by a large CTG repeat expansion) is rarely seen in the offspring of affected males.

Features of congenital MD include reduced fetal movements, contractures and polyhydramnios and may be detected prenatally. Affected neonates present with muscle weakness, hypotonia and respiratory difficulties. Congenital MD is associated with significant morbidity and mortality.

PND is available, but the disease severity is difficult to predict; large expansions of 500 or more CTG repeats are likely to cause congenital MD.

GENETIC IMPLICATIONS OF ABNORMAL ANTENATAL NEUROIMAGING

Antenatally identified brain abnormalities are always a considerable cause of concern for parents, and providing an aetiological diagnosis and prognosis is challenging for clinicians. CNS abnormality may be isolated or associated with cerebral or extracranial abnormalities. However, regardless of any associated abnormalities, the CNS malformation may be the major predictor of long-term outcome.

Table 1.6 Causes of Microcephaly

Cause	Inheritance/Comments
Genetic (Isolated)	AD, variable, mild/moderate delay to near normal for the family cognitive function
	AR, usually more severe and of prenatal onset
	X-linked, variable phenotype
Syndromic[a]	Chromosomal abnormalities (1p36 deletion)
	Microdeletion syndromes (Miller–Dieker syndrome)
	Single gene disorders (AD, AR and XL)
Environmental	Congenital infection (TORCH)
	Alcohol in pregnancy [Fetal alcohol syndrome (FAS)]
	Maternal phenylketonuria

[a]Microcephaly may be associated with
1. CNS abnormalities (agenesis of the corpus callosum, abnormal neuronal migration, cerebellar hypoplasia)
2. Extracranial abnormities (growth failure, congenital heart defect, structural eye abnormalities)

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; XL, X-linked; TORCH, Toxoplasmosis, Rubella, Cytomegalovirus, Herpes simplex.

Microcephaly

Microcephaly is defined as head circumference of two or more standard deviations below the mean. It should be taken into the context of the other fetal growth parameters as well as the head circumference of both parents. Environmental and genetic causes, syndromic and non-syndromic, should be considered in the differential diagnosis. The prognosis for the pregnancy and long-term development depends on the underlying cause (Table 1.6).

Holoprosencephaly

Holoprosencephaly (HPE) is the most common neurodevelopmental disorder arising as a consequence of the failure of the forebrain to divide into two individual hemispheres and ventricles. HPE has a prevalence of 1 in 250 embryos and 1 in 10,000 births. The extent of the brain malformation is variable and mild cases are difficult to detect by antenatal ultrasound scan.

Associated brain abnormalities include absent corpus callosum, absent septum pellucidum, absent or hypoplastic olfactory bulbs and tracts (arrhinencephaly) and optic bulbs and tracts, microcephaly, hydrocephalus, Dandy–Walker malformation and neuronal migration anomalies. Craniofacial abnormalities are seen in about 80% of patients ranging from severe, such as cyclopia and arrhinencephaly, to ocular hypotelorism, choanal stenosis, cleft lip and palate and single central incisor.

HPE is an aetiologically heterogeneous (Table 1.7) and phenotypically very variable condition. Virtually all individuals with abnormal cranial imaging have developmental delay, the degree of which is comparable to the severity of HPE. HPE microforms refer to the presence of mild craniofacial features (hypotelorism, ptosis, cleft palate, choanal stenosis, single central incisor) and are less likely to be associated with significant developmental delay. The recurrence risk depends on the underlying cause.

SHH gene product is the key signalling molecule in patterning of the ventral neural tube (10), the anterior-posterior limb axis (11) and the ventral somites (12). Whole gene deletions (chromosome 7q36) and point mutations are

Table 1.7 Aetiology of Holoprosencephaly

Aetiology	Condition	Comments
Chromosomal 25–50%	Aneuploidies: Trisomy 13 Trisomy 18 Structural chromosomal abnormalities: 13q deletion 18p deletion 7q deletion 13p duplication 2p deletion	Sporadic unless parent carrier of balanced chromosome rearrangement
Monogenic (non-syndromic) 25–40%	Sonic hedgehog signalling: *SHH, PTCH, GLI2* Nodal/TGF signalling: *TDGF1, FAST1, TGIF* *SIX3* and *ZIC2*	Monogenic with reduced penetrance Concomitant heterozygous mutations in two different genes in same or different pathways
Syndromic 18–25%	Smith–Lemli–Opitz Meckel Palister–Hall Rubinstein–Taybi	AR AR AD AD
Environmental	Maternal diabetes Alcohol Retinoic acid Cholesterol-lowering drugs	

Abbreviations: AR, autosomal recessive; AD, autosomal dominant.

implicated in the AD HPE with variable expression and reduced penetrance. A heterozygous mutation in this gene in conjunction with a heterozygous mutation in one of the genes involved in the nodal/TGF signalling pathway may give rise to HPE in non-Mendelian, digenic constellation.

Agenesis of the Corpus Callosum

Agenesis of the corpus callosum (ACC) consists of complete or partial absence of the white matter fibres that cross the midline between the two hemispheres (13). This is one of the most frequent brain malformations with an incidence of 0.5 to 70 per 10,000 (14). The incidence of ACC in children with developmental delay is estimated at 2% to 3% (15).

ACC may present as isolated condition or in association with additional CNS abnormalities such as abnormalities of neuronal migration and cortical development, including polymicrogyria (PMG), pachygyria, lissencephaly and heterotopias, as well as HPE, Dandy–Walker malformation, Chiari malformation and schizencephaly (15).

ACC is aetiologically heterogeneous. It can be caused by extrinsic factors such as maternal alcohol use in pregnancy or maternal phenylketonuria. It may also be associated with, usually unbalanced, chromosome rearrangements or part of an AD (HPE), AR (acrocallosal syndrome – duplicated hallux, postaxial polydactyly, aganesis/hypoplasia of the CC, dysmorphic features) or X-linked (Aicardi syndrome – ACC with chorioretinal abnormality) syndrome.

Fetal MRI is recommended to look for any additional CNS abnormalities, the identification of which could facilitate an aetiological diagnosis in about 25% of cases (16,17). (see chapter 3).

The prognosis for neurodevelopmental outcome in children with isolated ACC appears to be good in approximately 50% of patients although some may have transient difficulties such as neonatal hypotonia and speech delay. Approximately 25% of cases of isolated ACC may have mild to moderate learning and behavioural difficulties. Severe disability is usually associated with additional brain abnormalities, although these may not always be identifiable antenatally (15).

These figures should be used with caution as the available studies have limitations because of ascertainment bias and lack of standardised assessment protocol and long-term follow-up.

Ventriculomegaly

Ventriculomegaly (VM) indicates the presence of excess fluid in the lateral ventricles of the developing brain. Hydrocephalus is associated with raised intracranial pressure (ICP) and given that it is not possible to measure it in utero, the term VM is used in reference to fetal ventricular enlargement (18).

VM is diagnosed prenatally by means of ultrasound scan when the atrium width is larger than 10 mm, measured on transverse view just above the thalami (which corresponds to 4SD above the mean), from 14 weeks gestation to term (19). It is considered severe if the atrium width is larger than 15 mm, moderate between 12 and 15 mm and mild/borderline between 10 and 12 mm.

The incidence of VM ranges from 0.5 to 2 per 1000 births; isolated VM is seen in 0.4 to 0.9 per 1000 births (18). Associated abnormalities are reported in 70% to 83% of cases, 60% of which are extracranial (19,20).

VM is aetiologically heterogeneous and its natural history is variable. Amongst the non-genetic causes, congenital infection (Cytomegalovirus, *Toxoplasma gondii*, herpes simplex, although the latter is very rare with only about 100 cases reported in the literature) is identified in approximately 10% to 20% of cases of isolated, severe VM (21,22). Intracranial/intraventricular haemorrhage with consequent obstruction of the cerebrospinal fluid flow should also be considered, especially if VM occurs in the context of alloimmune thrombocytopenia (23), but it is otherwise rare.

Genetic causes include chromosomal abnormalities, AR, AD and X-linked syndromic conditions. Unbalanced chromosome abnormalities may be found in about 15% of cases of isolated mild/severe VM in the presence of other, intra- or extracranial abnormalities (Tables 1.8–1.10) (20). More than 100 single gene disorders may present prenatally with VM.

Table 1.8 Structural Abnormalities Associated with VM in Order of Frequency

Structural abnormalities	Frequency (%)
Aqueductal stenosis	30–40
Chiari II malformation	25–30
Callosal dysgenesis	20–30
Dandy–Walker complex	7–10
Other	5–10

Abbreviation: VM, ventriculomegaly. *Source*: From Ref. 24.

Table 1.9 Frequency of Chromosomal Abnormalities Associated with VM

	Abnormal chromosomes	
VM	Nicolaides et al., 2007	Weichert et al., 2010 (25)
Isolated	3–6%	Not reported
VM + other congenital abnormalities	25–36%	4.6%

Abbreviation: VM, ventriculomegaly.

Table 1.10 Syndromes Associated with VM

Syndrome	Inheritance	Features
Miller–Dieker syndrome	Microdeletion	Severe lissencephaly, microcephaly
Walker–Warburg syndrome	AR	Encephalocele, lissencephaly, myopathy
Seckel syndrome	AR	Microcephaly, intrauterine growth restriction
Apert syndrome	AD	Craniosynostosis, syndactyly of fingers and toes
Smith–Lemli–Opitz syndrome	AR	Microcephaly, urogenital abnormalities
Aicardi syndrome	X-linked	Agenesis of the corpus callosum

Abbreviations: AR, autosomal recessive; AD, autosomal dominant.

Aqueduct stenosis is the most common structural brain abnormality leading to VM (24). It may be secondary to congenital infection or intracerebral/intraventricular haemorrhage associated with aqueduct narrowing by a blood clot/scar. About 5% of cases are caused by mutations in the *L1CAM* gene on the X chromosome and are therefore more likely to affect males.

Fetuses with severe VM have a 2.2-fold (isolated VM) and 3.6-fold (VM associated with other abnormalities) increased risk of progressive dilatation compared to mild VM (25). Fetuses with asymmetrical bilateral isolated VM are more likely to have severe ventricular enlargements (25).

The outcome for the pregnancy and for long-term development depends on the severity of VM, underlying aetiology and the presence of associated abnormalities. Isolated, mild VM with normal chromosome analysis is expected to have good outcome in nearly 90% of cases (22,25). The risk of abnormal neurodevelopmental outcome is highest in the presence of associated anomalies irrespective of the degree of dilatation (91%) and in cases with severe isolated VM (68%) (25).

Severe VM develops with progression of the pregnancy and is therefore often diagnosed in the late second or third trimester and it is more likely to be associated with additional abnormalities indicating a poor prognosis (20).

Table 1.11 Causes of Structural Brain Abnormalities

Aetiology	Frequency (%)
Chromosomal	6
Single gene disorders	7.5
Polygenic/multi-factorial	20
Environmental/Teratogens	5
Unknown	>60

Abnormalities of Neuronal Migration and Cortical Development

Neuronal migration disorders and cortical dysplasia are the cause of severe, refractory epilepsy and global developmental delay in about 25% of cases (26). Conceptuses are at high risk of intrauterine death (IUD). Forty percent of infant mortality is caused by consequences of abnormal development of the CNS and the long-term morbidity, including developmental delay and epilepsy, has significant impact on the affected individual, family and the society. The aetiology is heterogeneous and summarised in Table 1.11.

Lissencephaly spectrum

Lissencephaly entails a continuum of abnormalities, from complete absence of gyri (agyria) to the presence of larger and fewer gyri (pachygyria). It is always associated with thickening of the cortex which is identifiable by MRI imaging. There is an increased incidence of ACC and cerebellar hypoplasia. AR and X-linked genes have been implicated. Some genotype/phenotype correlation has been observed.

Miller–Dieker syndrome. Miller–Dieker syndrome (MDS) is associated with severe lissencephaly, affecting the whole hemispheres, microcephaly and dysmorphic features. It is caused by a contiguous gene deletion of the terminal short arm of chromosome 17 (del17p13.3). Majority of cases are sporadic implying a low recurrence risk of 1%. Occasionally, the deletion arises as a consequence of a balanced chromosome rearrangement in one of the parents. This confers an increased recurrence risk for future pregnancies, the magnitude of which depends on the nature of chromosome abnormality in the parent.

Subcortical band heterotopia/DCX-related lissencephaly in males. Subcortical band heterotopia (SBH) is an X-linked disorder caused by mutations in the *DCX* gene on the X chromosome. The disorder primarily affects heterozygous females. The clinical picture ranges from mild learning difficulties to severe seizure disorder and developmental delay, depending on the extent of brain abnormality. Affected males present with lissencephaly, usually with an anterior to posterior gradient, severe global delay and infantile spasms. There is a 10% risk of germline mosaicism in mothers who test negative for the mutation identified in their affected son. Carrier female have a 25% risk of having an affected offspring at conception; if the offspring is male there is a 50% chance it will be affected.

Periventricular Nodular Heterotopia

PNH is a rare form of neuronal migration disorder presenting in females with uncalcified nodules of neurons subependymal to the lateral ventricles. It is caused by inactivating mutations

in the filamin A (*FLNA*) gene on the X chromosome. Affected male fetuses are usually not viable and die prenatally or in the neonatal period. The obstetric history of a carrier woman may reveal multiple miscarriages.

Eighty-eight percent of heterozygous females present with seizures (27) at an average age of 14 to 15 years, which in majority of cases have focal character. The severity may be variable, from rare seizure episodes not requiring medication to severe, difficult-to-treat epilepsy. Intelligence ranges from normal to borderline. The extent of radiological findings is variable and does not predict the severity of clinical phenotype.

The incidence of congenital heart disease (patent ductus arteriosus and bicuspid aortic valve) appears to be increased and stroke in young women has also been reported. The true frequency of the cardiovascular phenotype is not entirely clear and larger studies are required (28).

FLNA is currently the only known gene associated with PNH. Mutations are found in about 25% of singleton cases indicating that the condition is genetically heterogeneous. The mutation detection rate in clear X-linked pedigrees approaches 100%.

Mutations in *FLNA* are associated with four other phenotypes: oto-palato-digital syndrome type 1 and 2 (OPD1, OPD2), frontometaphyseal dysplasia (FMD) and Melnick–Needles syndrome (MNS). These conditions are characterised by skeletal dysplasia of variable severity in both affected males and females. PNH is usually not associated with these phenotypes.

Heterozygous women have a 50% chance of passing the gene in every pregnancy. Given the lethality in male fetuses, the risk of early miscarriage is close to 25%. PND, once the disease-causing mutation is known in the mother, is possible. The disease severity is not possible to predict, but it is important to emphasise that it can be variable. The unpredictability of disease severity may be a significant burden to prospective parents and families in making a decision about the pregnancy outcome.

Polymicrogyria

PMG is an abnormality of cortical development characterised by excessive number of gyri which are reduced in size. The distribution may be over the whole or only part of the brain surface thus defining the anatomically different forms of PMG. This is an aetiologically varied condition which may be isolated or part of a syndrome. Collectively, it is a relatively common abnormality of cortical development, although its true incidence is as yet not known.

The clinical manifestations range from mild neurological deficit to a severe encephalopathic picture, global developmental delay, visual impairment and refractory epilepsy, depending on the extent and distribution of cortical abnormality.

PMG may be caused by congenital infection (TORCH – Toxoplasmosis, Rubella, Cytomegalovirus, Herpes simplex) or impaired blood flow (twin-twin transfusion). The heritable forms of PMG are genetically heterogeneous, including syndromic and non-syndromic forms (Tables 1.12 and 1.13).

It is possible that rare AD and X-linked forms are clinically variable and may be inherited from an affected parent. Careful clinical examination of the parents for any mild neurological phenotype is therefore recommended and, if clinically indicated, followed by cranial MRI. Early PND is available if a genetic diagnosis is confirmed. The empiric risk for siblings of a singleton, non-syndromic cases is 5% to 10% if congenital infection and environmental causes have been excluded.

Table 1.12 Isolated (Non-Syndromic) PMG

Distribution	Inheritance	Gene
Bilateral frontal PMG	AR	Not known
Bilateral frontoparietal PMG	AR	GFR56
Bilateral perisylvian PMG	AD, AR, X-linked	Not known
Bilateral parasagittal parieto-occipital PMG	Sporadic	
Generalised PMG	AR	Not known

Abbreviations: PMG, polymicrogyria; AR, autosomal recessive; AD, autosomal dominant.

Table 1.13 Syndromic PMG

Syndrome	Inheritance
22q11 (Velocardiofacial syndrome)	AD
1p36 deletion	AD (rarely reproduce)
Aicardi syndrome	X-linked, only females
Fukuyama muscular dystrophy	AR
Muscle-eye-brain disease	AR
Walker–Warburg syndrome	AR
Joubert syndrome	AR
Zellweger syndrome	AR

Abbreviations: PMG, polymicrogyria; AD, autosomal dominant; AR, autosomal recessive.

Table 1.14 Outcome in ECM and DWC

	ECM		DWC	
Outcome	Isolated	Complex	Isolated	Complex
Favourable	97%	30–50%	12–40%	2%
Poor	3%	50–70%	60–88%	98%

Abbreviations: ECM, enlarged cisterna magna; DWC, Dandy–Walker complex. *Source*: From Ref. 32.

Posterior Fossa Abnormalities

Posterior fossa abnormalities (PFAs) include enlarged cisterna magna (ECM), Dandy–Walker malformation (DWM) and Dandy–Walker variant (DWV). DWM and DWV share many features and may be indistinguishable on prenatal ultrasound scan; the term Dandy–Walker complex (DWC) encompasses both DWM and DWV (29–13).

Approximately two-thirds of pregnancies with PFAs result in IUD or termination. Although isolated ECM and DWC are more likely to have a favourable outcome if the chromosome analysis is normal, the prognosis should be guarded (Table 1.14). Postmortem analysis of apparently isolated DWC identifies additional abnormalities in about 50% of cases and a specific genetic diagnosis could be established in approximately 30% (32).

Anencephaly and Neural Tube Defect

Isolated neural tube defect (NTD) and anencephaly are multifactorial conditions, product of an interaction between genetic susceptibility and environment. Both conditions can be readily diagnosed on antenatal scan. The preconception and early pregnancy folic acid supplementation has reduced the recurrence risk following a singleton case to 1% for either

Table 1.15 Causes of FADS

Condition	Inheritance
Neurogenic disorders	
Neurodevelopmental abnormalities	Chromosomal, AD, AR, XL, sporadic
Spinal muscular atrophy (SMA)	AR
Penna–Shokeir syndrome	AR
Cerebro-oculo-facio-skeletal syndrome (COFS)	AR
Myopathic disorders	AD, sporadic
Arthrogryposis multiplex congenital (Amyoplasia)	AD, AR, XL
Congenital myopathies	AR
Popliteal pterygium syndrome	AD
Congenital myasthenia	AR
Congenital myotonic dystrophy	AD
Restrictive dermopathy	AR
Maternal myasthenia gravis	Environmental
Oligohydramnios	
Teratogens	

Abbreviations: FADS, fetal akinesia deformation sequence; AD, autosomal dominant; AR, autosomal recessive; XL, X-linked.

anencephaly or NTD. The risk to the offspring of an affected parent is approximately 3% to 4%. Rare X-linked pedigrees have been reported in the literature (33) as well as AR (Meckel–Gruber syndrome, Nail-patella syndrome) and AD (Currarino triad) syndromes.

Fetal Akinesia Deformation Sequence

Restriction of fetal movement can result in a pattern of abnormalities recognised as fetal akinesia deformation sequence (FADS) (Table 1.15). Aetiologically, this is an extremely complex group of disorders often clinically identifiable in the second trimester of pregnancy. Careful neurological assessment of the mother is recommended. Definite PND is very difficult. This is also discussed in chapter 26.

PRENATAL DIAGNOSIS

PND is undertaken during pregnancy to determine the clinical or genetic status of the fetus. PND can use non-invasive or invasive techniques:

1. *Non-invasive diagnostic techniques*
   a. Prenatal ultrasound scan, 3D imaging and fetal dysmorphology
   b. Diagnostic imaging (MRI and spectroscopy)
   c. Free fetal DNA in maternal circulation
2. *Invasive diagnostic techniques*
   a. Chorionic villus sampling (CVS)
   b. Amniocentesis
   c. Fetal blood sampling – cordocentesis
   d. Fetal tissue sampling for diagnosis of rare skin disorders

Genetic Investigations

1. *QF-PCR* (quantitative fluorescence polymerase chain reaction) – for rapid detection of common aneuploidies
2. *Standard chromosome analysis* – identifies abnormalities of chromosome number and structure (deletions, duplications, translocations)
   a. If anomalies are identified on the antenatal scan and are not due to common aneuploidies
   b. One of the parents is a carrier of chromosome rearrangement
   c. Sibling with chromosome abnormality
3. *FISH* (fluorescent in situ hybridisation) – a test using fluorescently labelled probe for identification of microdeletion syndromes (e.g., MDS)
4. *MLPA* (multiple-ligation-dependent probe amplification) – a DNA-based, very versatile technique that can be tailored for detection of small deletions and duplications and can be used as a screening tool unlike FISH
5. *Array CGH analysis (comparative genomic hybridisation array; aCGH)* – a new technique to scan the genome for gains or losses of genetic material (deletions and duplications) at a much higher resolution level than standard- or high-resolution chromosome analysis. This test cannot detect balanced chromosome rearrangements.

   aCGH is increasingly used as a first-line investigation instead of standard karyotype in individuals with suspected genetic conditions. It has been very helpful for patients with learning difficulties and multiple congenital anomalies. De novo rearrangements involving gene-rich areas are likely to be significant and therefore of diagnostic value. Some rearrangements are relatively frequent, for example, 16p11.2 deletion of approximately 500 kb associated with learning difficulties, susceptibility to autism spectrum disorder and seizures, although their true incidence, and phenotypic implications are, as yet, not known.

   Some rearrangements, also known as copy number variations (CNVs) are familial and may be seen in phenotypically normal people as well as in individuals with problems suggesting that CNVs may contribute to genetic variations as well as play a role in the aetiology of complex diseases in an, as yet, not fully understood fashion.

   aCGH is currently not routinely used for PND given the limitations in interpreting the results. However, PND for a pathogenic deletion/duplication identified in a sibling may be offered to look for the specific rearrangement. These are more likely to have arisen de novo, carrying a low recurrence risk.
6. *Mutation analysis* is a single gene testing used when
   a. The fetus is at risk of a genetic disorder and the mutation in the family is known
   b. A known single gene disorder is suspected on the basis of the prenatal scan finding

GENETIC COUNSELLING

Genetic counselling is the process by which patients or relatives at risk of an inherited disorder are advised of the consequences and nature of the disorder, the probability of developing or transmitting it, the management aspects and reproductive options (34). Genetic counselling aims to provide:

1. Diagnosis, prognosis and/or risk estimation (clinical geneticist)
2. Psychological support before, during and after pregnancy regardless of whether a diagnosis has been established (genetic counsellor, clinical geneticist)

The prenatal diagnostic process often requires input from a number of professionals including the fetal medicine obstetrician, neurologist, neuroradiologist, paediatrician, surgeon and geneticist to establish a diagnosis and provide as accurate as possible information about the outcome of pregnancy and long-term outcome for the child.

Given the fact that a significant proportion of neurodevelopmental disorders are genetic, it is important that the

clinical genetics team is involved as early as possible as most genetic tests are time-consuming and often more than one test may be necessary.

Genetic counsellors are usually involved early on in the process to provide emotional and psychological support and facilitate the decision-making process when the outcome of pregnancy is considered. The counselling process may well extend to the next pregnancy.

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Imaging during pregnancy

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PRACTICAL CONSIDERATIONS

Imaging the nervous system during pregnancy can be challenging as there are multiple factors for consideration to ensure safety of both the mother and the fetus. Radiological examinations should be kept to a minimum at all stages in pregnancy unless there is a clearly defined indication; however, maternal well-being and management should not be compromised because of concerns about fetal exposure to ionising radiation.

POSITIONING

In the later stages of pregnancy, the patient may be at risk of aortocaval compression from the second trimester when in the supine position for even short periods of time. The gravid uterus can compress the aorta and inferior vena cava causing problems from mild hypotension to reduced cardiac output and cardiovascular collapse. This in turn can cause fetal distress. All women should have a wedge inserted under their right hip whilst in the supine position from the middle of the second trimester (1). Alternatively, women may be imaged in the left lateral decubitus position which prevents compression of the vena cava. Scanning times should be kept as short as possible to reduce maternal fatigue and discomfort (2).

DOSE

Computerised tomography (CT) brain imaging can be performed if clinically indicated and should not be avoided because of concerns about radiation. The natural background radiation dose to the fetus during pregnancy is approximately 1 mGy (3) and the fetal absorbed doses from head CT are less than 0.1 mGy. The estimated radiation exposure is thus low for CT when the fetus is outside the field of view and CT of the brain can be safely performed during any trimester of pregnancy.

The 1977 report of the National Council on Radiation Protection and Measurements (US) stated: 'The risk [of abnormality] is considered to be negligible at 0.05 Gy or less when compared to the other risks of pregnancy, and the risk of malformations is significantly increased above control levels only at doses above 0.15 Gy. Therefore, the exposure of the fetus to radiation arising from diagnostic procedures would rarely be cause, by itself, for terminating a pregnancy'. The 'risks of pregnancy' referred to in this statement include the normal risks of pregnancy: 3% risk of spontaneous birth defects, 15% risk of spontaneous abortion, 4% risk of prematurity and growth retardation and 1% risk of mental retardation (4).

CT CONTRAST

Intravenous contrast crosses the placenta and into the fetus. There are no controlled studies on its effects and so a risk–benefit analysis should be conducted before use (5).

There have been concerns in the past about neonatal thyroid function after the administration of iodinated contrast media in pregnancy (12). Recent studies have shown that a single high-dose exposure is unlikely to have a clinically important effect on thyroid function at birth (13).

MAGNETIC RESONANCE IMAGING (MRI)

There is no scientific evidence to suggest that there is a significantly increased risk to the fetus in the first trimester when performing a routine MRI examination but because this is the period of active organogenesis, MRI should be avoided unless the potential benefits outweigh the theoretical risks (2). MRI has been used to evaluate obstetric and fetal conditions for over 20 years with no evidence of adverse effects (6). Some authorities do raise safety concerns due to the heating effects of radiofrequency pulses and the effects of acoustic noise on the fetus (7), and more research is needed.

Overall, the clinical need for imaging should be addressed and whether MRI is appropriate to answer the clinical question. Pregnant patients should be informed that there is no evidence that MRI imaging during pregnancy has resulted in deleterious effects to the developing fetus (11).

MRI CONTRAST

The safety of using intravenous contrast agents in pregnancy is not clear (7). Intravenous gadolinium-based contrast has been shown to cross the placenta and appear within the fetal bladder (8,9). It then enters the fetal bloodstream, is excreted into the amniotic fluid, swallowed by the fetus and reabsorbed from the gastrointestinal tract. The half-life of the drug in the fetal circulation and the effect of this drug on the developing human fetus are unknown (8,9). In animal studies, growth retardation and delay in ossification have been reported after administration of a high dose of the drug (10). The safety of intravenous administration of the drug in pregnant patients has not been widely tested and established (8,9). Therefore, use of the drug is generally not recommended in pregnant patients (8,9).

NEUROLOGICAL CONDITIONS

Headache

Headache is a common complaint and is prevalent in pregnancy. Neuroimaging (including CT and MRI) may reveal an underlying aetiology for headache in 27% of cases including cerebral venous sinus thrombosis, intracranial haemorrhage and posterior reversible leukoencephalopathy (14). The chances of having an intracranial pathology on neuroimaging have not been proven to be higher when there is positive neurology on clinical examination (14).

Pre-Eclampsia/Eclampsia (Fig. 2.1)

Indications for imaging. Neuroimaging may not be needed if the clinical picture is clearly defined. The diagnosis of eclampsia is made when pre-eclampsia is complicated by seizures in the absence of other causative conditions (15). However, if there is focal neurology or any deterioration in neurological status, imaging may be useful.

Modality and protocol. MRI is the superior imaging modality (20) with the most frequent abnormality seen on T2 and FLAIR sequences. Parieto-occipital hyperintense cortical/subcortical lesions are seen in 95% of patients (21). CT may be useful to rule out haemorrhage if MRI cannot be performed. Diffusion-weighted imaging can be useful in distinguishing reversible vasogenic oedema from infarction/cytotoxic oedema (16,18). This technique, if there is an early diagnosis of ischemia, may be helpful in predicting whether there will be an adverse outcome (18).

An MRI protocol should consist of T2, T1, FLAIR and DWI sequences. Gradient echo and contrast-enhanced sequences could also be performed but are not essential. The imaging should be repeated once the symptoms have resolved and the blood pressure has normalised.

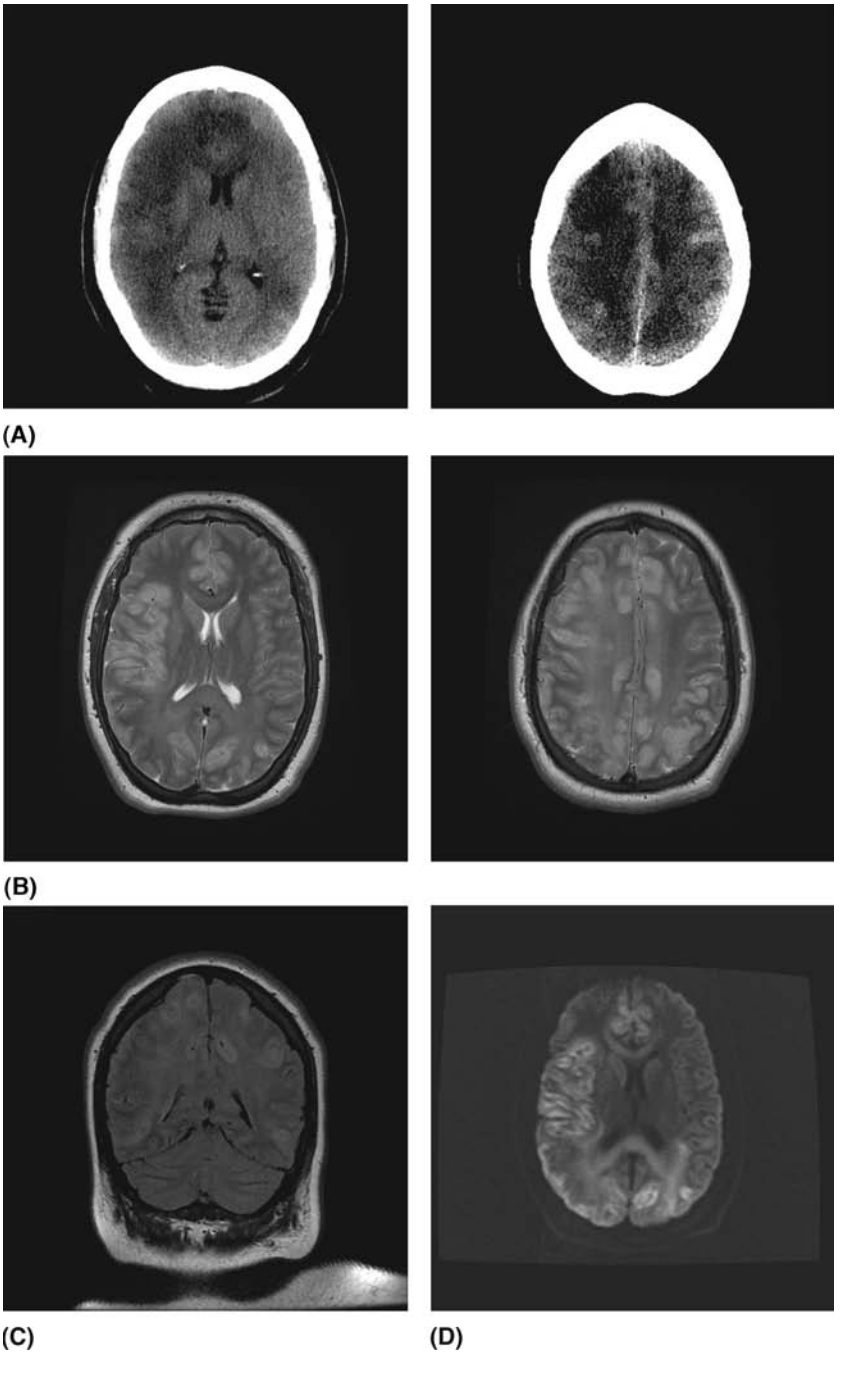

Figure 2.1 A 22-year-old pregnant woman with HELLP syndrome with a decreased Glasgow Coma Scale and dilated pupils. **(A)** CT brain (without contrast). Diffuse predominantly white matter low attenuation can be seen, more extensive on the right with mild mass effect. **(B)** Axial T2-weighted MRI. **(C)** Coronal FLAIR. **(D)** Axial diffusion. Cortical and subcortical T2 and FLAIR hyperintensity in parietal and occipital lobes and to a lesser extent the frontal lobes. Some of these lesions show restricted diffusion (low signal was seen on the corresponding ADC map). Appearances are consistent with eclampsia.

Findings. There is considerable clinical and radiological overlap between reversible posterior leukoencephalopathy syndrome, hypertensive encephalopathy and eclampsia (18).

CT Focal regions of asymmetric hemispheric oedema/hypodensity. There is a predilection for the posterior circulation with the parietal and occipital lobes most commonly affected, followed by frontal and inferior temporal lobes and cerebellum (16,18,20). The changes may be transitory (19). This resembles a watershed distribution with cortex and subcortical and deep white matter involved to varying degrees (16,18). The basal ganglia may be involved (19,20) but the brainstem is rarely of abnormal signal (20,21). Associated petechial haemorrhage can occur (19); haemorrhage is said to occur in 15% (16).

MR T1 hypointense, T2 and FLAIR hyperintense cortical/subcortical lesions. T2* punctuate low-signal lesions if haemorrhage is present (20). The DWI is usually normal with a high ADC value suggesting vasogenic oedema which usually completely reverses (16,20). Focal areas of restricted diffusion with high signal on the DWI with normal or decreased ADC are uncommon and may indicate irreversible infarction (16,20). If intravenous contrast is given there is variable enhancement (21). MR spectroscopy, although not routinely performed, may show widespread abnormality with increased choline and creatine and mildly decreased *N*-acetyl aspartate (NAA) that usually returns to normal within 2 months (20,21). MRA may show narrowing of the major intracranial vessels which can resolve with time (20).

Eclampsia may result in a posterior reversible encephalopathy syndrome. This is probably due to a multitude of factors including cytotoxic effects on the vascular endothelium and labile blood pressure which can lead to breakdown of the blood–brain barrier in the posterior circulation (17).

Cerebral Venous Thrombosis (Fig. 2.2)

Patients with cerebral venous thrombosis (CVT) in pregnancy tend to be younger and to present more acutely than patients

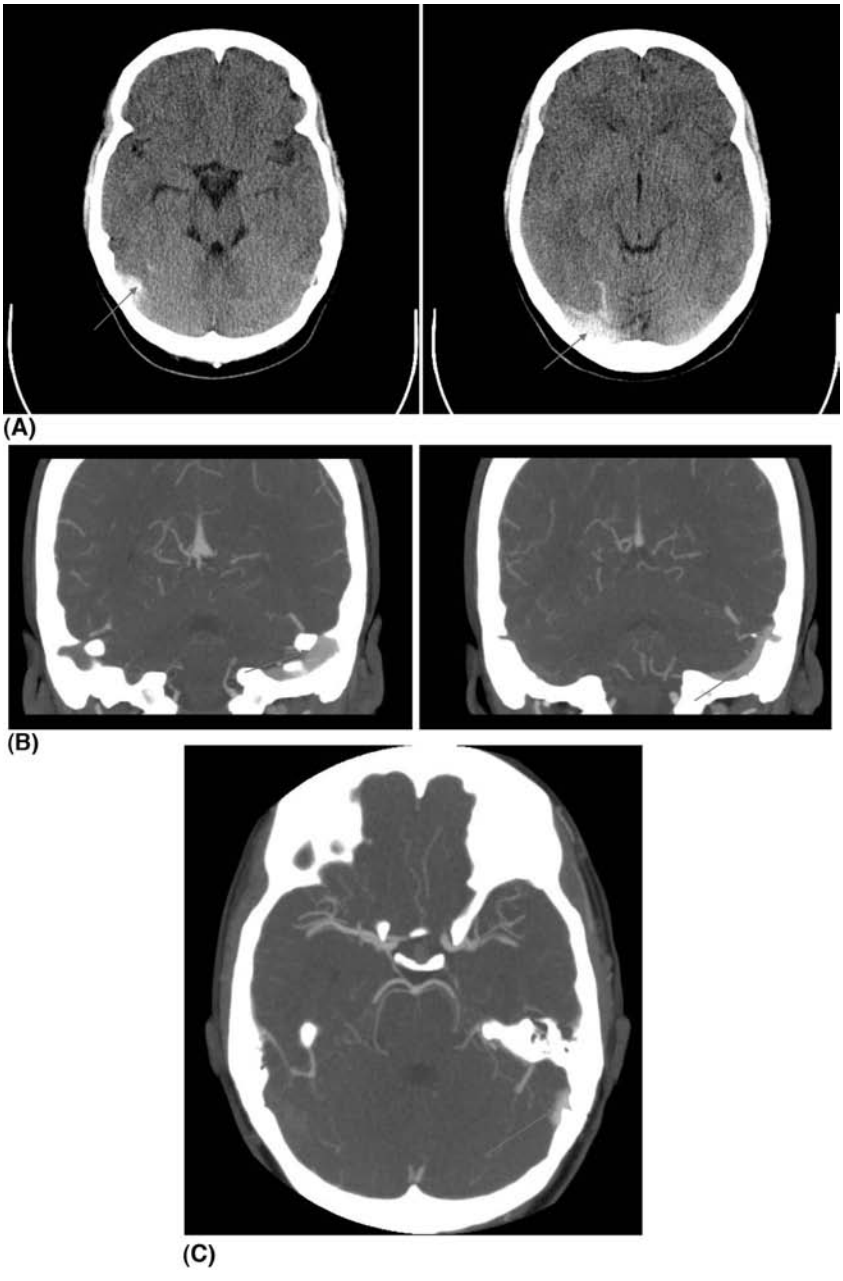

Figure 2.2 A 28-year-old woman who whilst 16 weeks pregnant developed sudden onset of headache and nausea. **(A)** CT brain scan showing hyperdense transverse and sigmoid sinuses. **(B)** coronal and **(C)** axial CT venograms demonstrating that there is no filling of the right lateral transverse sinus and sigmoid sinus due to venous sinus thrombosis.

with non-obstetric causes. Symptoms also tend to reach a plateau within 10 days of symptom onset compared to a longer course which could be progressive (23). There has been found to be no difference in the presenting neurological symptoms or radiological findings between the two groups but the outcome has been proven to be better in obstetric patients (23). Intracranial veno-occlusive disease is most common in the first 3 weeks following delivery (16).

Indications for imaging. Imaging should be performed when patients present with symptoms such as headache, confusion, decreased level of consciousness, and papilloedema when other potential causes have been excluded. Focal neurological deficit may reflect the venous sinus or cerebral vein involved (19) and if present it would be a strong indication for imaging. CVT can result in focal brain swelling and venous oedema or infarction due to raised venous pressure (25). There is poor correlation between extent of parenchymal changes and location and degree of clot (24) – probably due to collateral circulation.

Modality and protocol – CT versus MR venography. Brain imaging by itself is of little diagnostic value in CVT as it can be normal in 25% of cases especially in the acute stage. MRI is more sensitive than CT in early detection of thrombosis and more accurate in depicting the extent of the clot and any possible complications (25). Parenchymal changes are seen on MRI in 40% to 70% (22). Lack of enhancement of a sinus on CT/MRI is an early sign (21). MR venography (MRV) may not be able to differentiate between thrombosis and hypoplasia and is not sensitive in the diagnosis of cortical vein thrombosis (23). CT is quicker and therefore more tolerant of patient movement.

CT with CT venography (CTV), both with thin sections, is recommended as the initial screening examination. MRI (T1, T2, T2*, DWI) with phase-contrast MRV can be performed if the CT is negative. Intravenous gadolinium is relatively contraindicated in pregnancy.

Findings

CT This may show hyperdensity in the dural venous sinuses, cortical veins ('cord sign') or deep cerebral veins, but there is low sensitivity due to slow flow (30,31). The dense vein sign is seen only in 20% to 55% of cases and is insensitive in chronic cases (25). In the parenchyma there may be signs of mass effect with sulcal effacement and/or venous infarcts, which do not conform to arterial vascular territories and may include areas of haemorrhage (24). However, these changes are not sensitive or specific (24). If the straight sinus or internal cerebral veins occlude, the thalami and basal ganglia may be hypodense (20,21). It may take 7 to 10 days after symptom onset for the empty delta sign (seen on post contrast imaging) to be detected on CT (20,30). Thick sections may miss both the hyperdense sinus or vessel and the 'empty delta sign' (24).

MR T1: Acute thrombus is isointense. Subacute thrombus becomes hyperintense (21).

T2: The clot is initially hypointense then becomes hyperintense and isointense in the chronic stage (21). A venous infarct has mass effect with mixed hypo/hyperintense signal in the adjacent parenchyma (21).

FLAIR: The thrombus is hyperintense and venous infarcts are of high signal.

T2*: The thrombus is hypointense and 'blooms' (21). Parenchymal and/or petechial haemorrhage is of low signal (21).

DWI: In ADC/DWI parenchymal changes are variable and heterogeneous with a mixed picture of cytotoxic and vasogenic oedema (21). The parenchymal changes are more often reversible than in arterial occlusions (21).

MRV: absence of flow in occluded sinus. Collateral vessels may be seen (21). Phase-contrast MRV is not limited by hyperintense thrombus (21).

High signal in sinuses on T1, T2, FLAIR is a reliable sign (19). Filling defects following administration of gadolinium may develop within the first week (22). Imaging should be performed in axial and coronal planes so flow can be analysed perpendicular to the axis of the sinuses (24).

The sensitivity of T2* and T1 in the first 3 days is 90% and 71%, respectively. For cortical veins T2* has 97% detection compared with 78% on T1 (27). T2* provides the highest detection of cortical vein thrombosis followed by T1, FLAIR, and time-of-flight MR angiography (MRA), with sensitivities of CT and CT venography below 30% (27). Between days 1 and 5, isointense T1/hypointense T2 findings are due to deoxyhaemoglobin. Between days 5 and 15, hyperintense T1/T2 findings are due to extra cellular methaemoglobin, initially peripherally then centrally (27).

The main limitation is the similarity in signal of flow artefacts with acute thrombus (isointense T1, hypointense T2) (23). It is necessary to perform T1 and T2 in orthogonal planes to distinguish slow flow from thrombus (23). Other limitations are that absence or hypoplasia can simulate occlusion (30). Phase contrast is useful as it is dependent only on phase shifts engendered by moving blood (30).

Contrast MR venography can help but is contraindicated in pregnancy and not good in detection of chronic thrombosis (24,26).

Venous oedema/ischaemia is represented by high T2 signal which may persist up to 2 years and may eventually lead to infarction (24).

T2 high signal is usually subcortical but may involve cortex (28).

Haemorrhage is shown by low T2 signal early which extends from centre to periphery unlike arterial infarcts (29).

Haemorrhage in venous infarcts usually has extensive surrounding low attenuation in contrast to primary haemorrhage (29).

Peripheral gadolinium enhancement may look tumour-like (28).

Commonly, multiple sites are involved with more swelling than arterial infarcts (29).

Subarachnoid Haemorrhage

Indications for imaging. The risk of subarachnoid haemorrhage (SAH) is five times greater in pregnant than in non-pregnant women (15,19), and rupture of an intracranial aneurysm is the most common cause. Pregnancy-induced hypertension has also been linked to acute subarachnoid haemorrhage (19).

Modality and protocol. CT with CT angiography (CTA) is the gold standard for the initial investigation of subarachnoid haemorrhage due to its high sensitivity to acute SAH, short scan times and widespread availability; however, MR with MR angiography (MRA) allows assessment without the need for ionising radiation or intravenous contrast (15,32). The sensitivity of CT however drops rapidly with time with 95% positive within the first 24 hours dropping to less than 50% by 1 week (21) and approaching 0% at 3 weeks (32). Multi-slice CTA is 90% to 95% sensitive for detecting an aneurysm that measures 2 mm or greater (21). Lumbar puncture should be performed in all cases of suspected SAH if there is no clinical contraindication.

MR may be able to supplement CT in the subacute phase when the sensitivity falls or when the LP is inconclusive (32).