

1

INTRODUCTION

Philip M Preece

It has been almost 70 years since rubella was suspected of being a human teratogen (an agent capable of inducing birth defects), and, in that time, much has been learned about how prenatal influences can affect the normal development of the embryo and fetus (Gregg 1941). In the 1960s and '70s, these concepts were expanded to the field of behavioural teratology, when it was observed that prenatal exposure to certain agents or conditions could influence later behaviour and function in the offspring even in the absence of any obvious physical deficit. More recently, the idea of fetal programming has been proposed, whereby conditions during pregnancy (e.g. undernutrition) can have long-term effects on the health and well-being of the offspring. Such conditions might, for instance, increase the likelihood of diabetes, obesity and cardiovascular disease (Barker 2000, Godfrey and Barker 2001). Clearly, a range of factors can influence embryonic and fetal development, affecting both physical and functional status in the offspring.

Scope of the book

This book firstly documents the consequences of intrauterine exposure to various drugs and substances of abuse. Next, we hope to demonstrate the complexity of the subject, as the raw effects of exposure to such chemicals in utero are modified or influenced by a wide range of pre-, peri- and postnatal factors.

In exploring the range of challenges to understanding this complex subject, we seek to provide the research base available in the literature. This should provide, for the practitioner, the basis for making decisions about the care and management of these children with some security and at as early a time as possible. Professionals need to provide active medical and social interventions, in addition to protective management, to prevent vacillation and delay in the appropriate and effective care of these children (Department for Children, Schools and Families 2008).

Prenatal factors

Children's development and emotional security are intimately connected to parental factors and the circumstances of their birth. A multitude of parameters influence the success of this process in normal circumstances (Fig. 1.1). It is self-evident that many childhood features reflect parental genetic make-up. There are significant risks in a range of conditions in which mothers may need or choose to take medications and drugs in pregnancy. Epilepsy and learning disability (North American terminology: mental retardation) have a variable

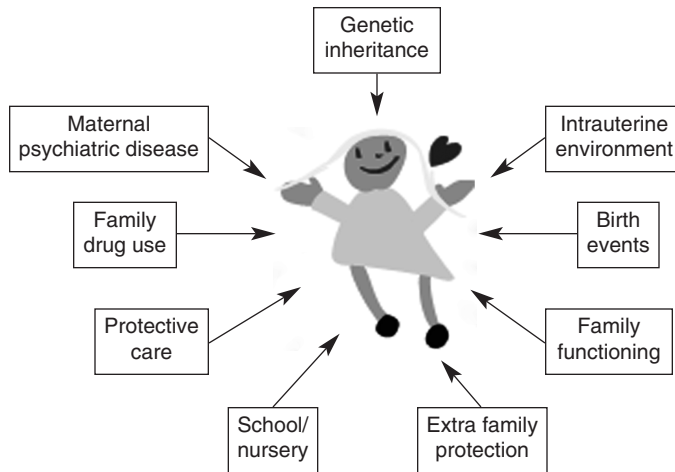


Fig. 1.1. Cumulative effect on infant development.

heritability and may also mean exposure of the infant to maternal medication. Psychiatric disease such as depression and psychosis may require treatment in pregnancy but both of these conditions may also have a significant effect on maternal parenting skills and subsequent infant development, particularly in language development irrespective of any potential intrauterine effect of the drugs used in treatment (Orr and Miller 1995, Murray and Cooper 1997). Maternal ill health and nutritional deficiency during pregnancy can have a significant effect on fetal growth and development, which may be compounded by smoking, drugs of abuse and alcohol use in pregnancy (Maughan et al. 2004).

Parents who take drugs such as opiates or misuse alcohol may have additional difficulties, predisposing them to their choice of lifestyle, including a range of neurodevelopmental and mental health problems (Kennare et al. 2005). Mothers who abuse alcohol and drugs often do not care well for themselves in pregnancy, and their chaotic lifestyles do not allow for optimum health (Guerrini et al. 2009). Such women may also be exposed to blood-borne viral infections such as hepatitis and human immunodeficiency virus, which may be transmitted to the fetus (Bell and Harvey-Dodds 2008). Some intrauterine pharmacological agents cause poor fetal growth and premature labour and expose infants to the complications of preterm birth and low birthweight. The effects of smoking, alcohol and drug use may also be cumulative (Riley and McGee 2005).

Postnatal factors

Major concerns arise in infants of drug- and alcohol-abusing mothers. Not only are there the potential risks of intrinsic neurodevelopmental problems, explored in the subsequent chapters of this book, but there are also the real risks of family disharmony, domestic violence, physical and emotional abuse and neglect (Advisory Council on the Misuse of Drugs 2003). Such dysfunctional families provide unique challenges to the statutory agencies

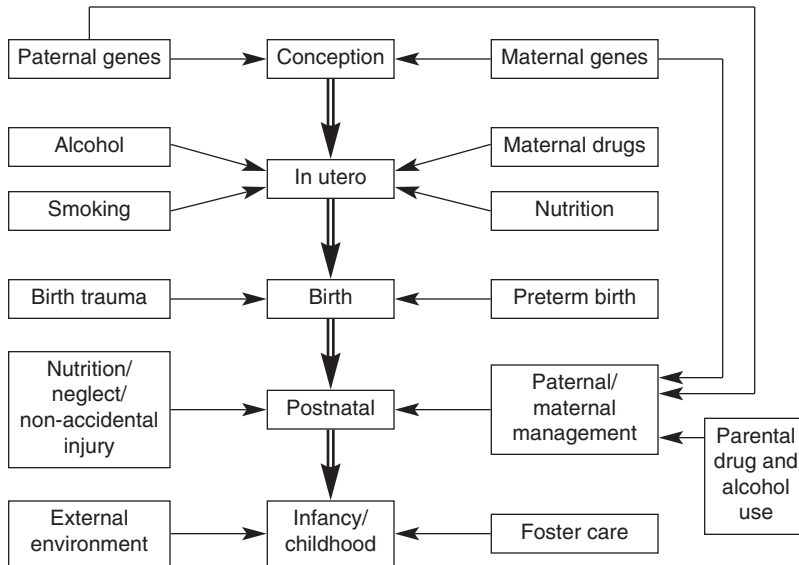


Fig. 1.2. Factors influencing infant development.

designed to protect children. These families move frequently, associate with a wide range of individuals who are often fellow drug abusers, use unsuitable carers, disengage with social and primary health care services, and may obstruct efforts to supervise and protect children (Fig. 1.2).

As will be seen throughout this book, disentangling the primary effects of the intra-uterine exposure from genetic predisposition and the subsequent family environment needs particularly careful research and large numbers of families to study, to control for all the potential confounding factors. For example, very few mothers who abuse drugs do so with single agents, more often mixing these with the effects of alcohol and smoking (see Chapter 8). Recreational drugs are often taken intermittently, making the study of the effects of amphetamines and ecstasy difficult to evaluate, as it is well known that teratogenic effects will vary at different times in gestation. Finally, children cannot be left in the family home if they are at clear risk of further harm. As a result, many studies are compromised by the need to accommodate children at different postnatal stages when home circumstances demand the child be protected.

These vulnerable children are often very difficult to place with suitable foster carers and provide enormous challenges to even the most experienced childcare specialists. The current drive to place children ‘looked after’ (i.e. fostered) as early as possible in adoptive placements, to minimize the risks of frequent changes of foster carers, may result in placement at an early age when the pattern of neurodevelopmental problems may not be fully expressed. As a result, adoptive placements with well-meaning but frequently inexperienced parents pose further challenges for post-adoption support.

Effect of intrauterine exposure

This book is designed to inform the reader of the potential risks to infants exposed to a range of intrauterine chemicals, which are potentially neuroactive, medicinal drugs such as antiepileptics, antidepressants and antipsychotics, and recreational drugs/drugs of abuse such as alcohol, opiates, cannabis and tobacco. We review the teratogenic action of some of the chemical processes and the relationship to the stage of pregnancy of exposure. Not all of these agents alter anatomical structure, however. Some may alter the chemical balance of neurotransmitters and affect the regulation of brain function in both the short and long term (Stanwood et al. 2001). These changes may have profound effects on children's behaviour and propensity to behavioural disturbances, forcing changes in parental strategies for dealing with potentially challenging behaviours. Birth parents retaining custody of their children, while already struggling to deal with the many challenges in their own lives, often encounter additional difficulties managing an irritable child with potential problems such as the withdrawal symptoms of neonatal abstinence syndrome. Those children who are in the care of statutory agencies will pose different challenges to foster carers who may question their own parenting strategies when confronted with a very difficult child and, if not well informed of the likely effect of the child's previous exposure, may feel inadequate as parents and carers. Some children from very troubled backgrounds will need more than the love and security the average family can provide and need 'super parents' with a wide range of support packages to ensure family stability. We explore strategies to support families with these children and provide statutory agencies with the information to assess when to intervene to protect children from harm.

The following case study illustrates the complexity of the subject. It concerns a child exposed to a potentially toxic agent in utero, describing the impact a wide range of factors had on the individuals in her family and how their lives were affected by the circumstances in which they found themselves, and details the efforts of her parents, advisors and statutory agencies to protect her from a range of potentially damaging factors.

Case history

M was her mother's fifth child. The mother was identified as a heavy drinker and was consuming at least 8 units (64g) of alcohol per day. At birth (at 38 weeks' gestation) M weighed 1.94kg and had a ptosis of the right eye and bifid uvula. No other abnormalities were noted at the time. She had mild hypoglycaemia (minimum blood sugar level 2.4mmol/L) despite tube feeding. Discharge was delayed as the mother appeared drunk on the unit. Enquiry to Social Care revealed two previous children who were in the care of the maternal grandmother, but the parental partnership was strong and there was no reason to further delay discharge from the neonatal unit.

M then had a stormy period of three admissions to hospital within four months with poor weight gain and feeding. On one occasion, the general practitioner queried the quality of home care. The failure to gain weight by 4 months prompted a more detailed look at M, and clinical examination suggested features of fetal alcohol syndrome (FAS) with short palpebral fissures, flat philtrum and thin upper lip associated with faltering growth, ptosis and bifid uvula. Investigations with routine metabolic screen and chromosome analysis were

normal, while cerebral ultrasonography revealed an isolated right cerebral cyst. Tube feeding was started and there was an initial weight gain. The mother had been referred to a psychiatrist three months after M's birth for treatment of alcoholism and attended once, but thereafter did not attend.

Following home tube feeding with the supervision of the community paediatric nurse, M's weight and growth improved from the fourth to the sixth month of life. There was one incident when she was seen with an unusual pattern of bruising which was explained by the use of a damaged child's bouncing seat. However, at 6 months growth was again faltering and Social Care had become concerned by the level of care in the home and organized a strategy meeting of all the professionals involved. It was agreed to proceed to a formal child protection conference under the UK Children Act (1989). Before the meeting could take place, an incident occurred at home where the mother was severely injured in a domestic dispute with the father and was admitted to the hospital. The father subsequently disappeared and was found contemplating jumping off a motorway bridge into traffic. M was admitted to hospital care and the opportunity taken to refer her to have a gastrostomy fitted to maintain long-term enteral feeding. The child protection conference agreed that M should be placed in foster care and the two other children at home placed with family members. Developmental assessment at this stage suggested normal psychomotor development. While in foster care, M stayed with the parents six hours per day, four days per week in an attempt to assess maternal function and reintegrate her into the family home. At 13 months she started to have breath-holding attacks and reflex anoxic seizures. She was a very active girl and was on the go continuously once she was independently mobile. She had a very variable sleep pattern and she was transferred to alternative foster carers who could manage better with her continued restlessness. Her mother continued to drink and the home situation continued to cause concern until eventually the siblings, who had returned home, were accommodated with the maternal grandmother.

Detailed developmental assessment at 20 months revealed that while motor development was progressing, other aspects of development, particularly speech, were now seriously delayed, and assessment was severely impaired by poor concentration and hyperactivity. Growth parameters were still below the 0.4th centile for height, weight and head circumference. At this point, Social Care told the parents that reintegration was not a realistic possibility, and the mother decided to make a serious attempt to stop drinking reinforced by regular monitoring of liver function. Social Care now had a dilemma, and the children's guardian ad litem (a court appointment under English law to represent the interests of the child) recommended a last attempt to reintegrate M within the family so long as the mother continued to abstain and could provide a structured home environment. M moved to new foster parents while the reintegration plan was explored, and she was again placed with the birth family at 2 years 6 months and removed from the child protection register. She still presented as a very active child with limited attention span and delayed expressive speech. By the age of 2 years 11 months, a Griffiths developmental assessment demonstrated normal motor development but speech at a 15-month level and hand/eye coordination at an 18-month level.

When M was 3.5 years old her mother relapsed and was warned by Social Care that any deterioration in maternal care would result in the children being removed, once again,

from the family home. At 4 years 3 months, one of her siblings was injured and M and her elder brother were removed from the home for their safety to the grandparents' care. Unfortunately, the grandfather died suddenly less than a year later and as her grandmother could not manage M's care on her own she was again placed with foster parents. All the changes in family circumstances had up to now inhibited active management of M's increasingly difficult behaviour. She was placed in a special school for children with moderate learning difficulties. She was described as very active with impulsivity, flitting attention, and autistic features of indiscriminate affection, solitary play and lack of imaginative play thought to be characteristic of the developmental pattern of attachment disorder in the context of FAS.

A formal assessment of attention skills was initiated but a recommendation that medical treatment should be offered was held up, as the parents still retained parental responsibility and Social Care was required to seek their permission.

An application for a freeing order, to allow adoption, was opposed by the family, who made a further application for residence with the grandmother. While this was rejected, it further delayed the opportunity to finalize M's adoptive placement, which was only finally agreed at 6 years 4 months. The foster parents, by now, needed regular respite care, and the prospective adopters withdrew at 6 years 9 months. By this time, M was described as having no awareness of danger, self-harming when frustrated and with an erratic sleep pattern in addition to her other problems. At this stage the foster parents and Social Care agreed to a trial of long-acting methylphenidate with some benefit. Finally, she was confirmed in her long-term placement under special guardianship arrangements and care was transferred to another unit close to the guardian's home and her new school at the age of 7 years 6 months.

Complexities of care

M's story was an enormous education to all the professionals working to protect her future and illustrates vividly the complexities of care for these vulnerable children. She had two parents who were impulsive and volatile even when they were not drinking. They lived a chaotic lifestyle exacerbated by frequent domestic disputes and violence. M also suffered from the teratogenic effects of exposure to alcohol in pregnancy, and then was subjected to physical abuse and neglect. She also was vulnerable in a system which attempted to keep the family together, whereas the parents were too dysfunctional to provide her with the security and structure needed to ameliorate the effects of FAS. Once she became a 'looked after' child, she was moved to a range of carers before eventually finding an adoptive placement at 7 years of age. By this time, many of her behaviour patterns were already ingrained and difficult to change. It is clear that she was a victim not only of FAS but also of a care system which, despite the provision within the Children Act (1989) that "the child's interests are paramount", found it difficult to weigh up the balance between her best interests and the interests of her family and society as a whole. It is clear that she will continue to challenge the support services available even in a highly developed country such as Britain.

How could we have intervened in M's interests at a point when she could be protected from the secondary risks of disadvantaged children? It is possible in some circumstances,

when forewarned, to minimize the exposure to alcohol in utero by early work with alcohol-abusing mothers (see Chapter 13). A prebirth child protection case conference would now be the norm in these circumstances, and social care and health workers could devise appropriate strategies to intervene with intensive support and monitoring when M's care fell below acceptable standards (see 'Thresholds for intervention', Chapter 12). Early legal procedures could, using a supervision order, allow her to stay with the family, while maintaining a degree of coercion with clear criteria for intervention. Adoption legislation in England and Wales now allows 'twin tracking' so that time is not lost waiting for circumstances to declare themselves before final decisions about placement are made, and there are now standards regarding timescales to avoid the drift illustrated in this case history. There are still uncertainties in the legal system though, and the presumption of 'kinship placements' within The Children Act (2000) can complicate decisions, as illustrated in M's case. However, a thorough knowledge of the natural history of FAS, as outlined in Chapters 6 and 7, could have predicted her high level of need and the probable failure of her placement with family members who, at best, were not in robust health, and who also had some ambivalence to the parental problems, which clouded their judgement.

Behavioural teratogenesis

Maternal alcohol ingestion represents the archetypal form of behavioural teratogenesis, causing not only physical malformations but also disruption of brain development, significant impairments in behaviour, attention control and language development, and an increased risk of offending behaviour in later life. However, a similar process may occur in a range of circumstances where infants are exposed to a variety of neuroactive substances, therapeutic drugs and drugs of abuse.

Antiepileptic drugs (AEDs) are necessary to control epilepsy in adults, and pregnancy poses additional risks for women with epilepsy (EURAP Study Group 2006). Fetal hydantoin (phenytoin) syndrome has been well described for many years, but the newer range of AEDs is now more commonly used, including carbamazepine and sodium valproate. The long-term outcome for the commonest medications currently in use to treat seizure disorders described in Chapter 4, but we need to continue to monitor the outcome of pregnancies where the newer AEDs such as lamotrigine, topiramate and levetiracetam are being used as 'safer' alternatives in the management of the more complex forms of epilepsy. However, in view of the most recent studies there is a need to consider whether all adolescent girls should consider a switch of treatment from valproate to prevent potential problems, especially since a significant number of pregnancies in young women are unplanned (Tomson 2009).

In the last 20 years, a wide range of medications has been introduced for the management of serious psychiatric diseases such as depression and psychosis, with significant improvement in the quality of life of the sufferers. However, these drugs are complex and may affect fetal development. Their long-term effects are difficult to quantify as they are less understood than other medications. Clearly there is a need to minimize the risk by withdrawal of the medication, if possible, but there are real risks to the mental health of mothers and the safety of the infant postnatally with inadequate treatment. The risk of infanticide, abuse and neglect should not be underestimated (Orr and Miller 1995), and it is probable

that the use of medication to minimize symptoms is preferable to the risks of no treatment (see Chapter 5).

FAS has been well described, and the problems of alcohol use were even highlighted in ancient times and graphically illustrated by Hogarth in 18th century London (although there are other interpretations of these works) (Calhoun and Warren 2007). The morphological features and presentation in young children, and the lasting implications and characteristic neurobehavioural patterns in older children and adolescents, are now widely recognized in typical cases. What has only recently started to be understood is the wider spectrum of intrauterine alcohol effects without the characteristic morphological pattern, i.e. fetal alcohol spectrum disorder (Calhoun et al. 2006). The dose and frequency pattern related to severity of effect is still not clearly delineated, and the difficulties of measuring the dose/effect response are elegantly highlighted in Chapter 2. Concerns have been raised about the effect of low levels of alcohol exposure and, more importantly, the effect of binge drinking, resulting in the emerging consensus that there is no 'safe' level of exposure (Department of Health 2007). We are now developing a clearer understanding of the critical effect of alcohol and other teratogens on the developing brain in very early pregnancy before the completion of embryogenesis with resultant structural changes to the brain. We are also developing an understanding of the complex mechanisms for continuing damage in later pregnancy through a host of different mechanisms including dendritic pruning, apoptosis and epigenetic factors (Gemma et al. 2007).

Acute withdrawal effects of opiates are a common reason for admission to neonatal units in developed countries, and the relationship of exposure to cocaine, heroin and methadone use in pregnancy and withdrawal is well understood (Advisory Council on the Misuse of Drugs 2003). Large-cohort studies in some populations are now describing longer-term effects of crack cocaine (Chapter 8), but particular attention needs to be given to potential confounding factors such as exposure to other agents in utero, e.g. cigarettes, alcohol and recreational drugs like cannabis (Chapter 9). Mothers who abuse opiates do not always take care of their own health antenatally (Kennare et al. 2005), and the infants are often raised in less than ideal family circumstances, with a significant number being accommodated with foster families, further clouding the validity of observational studies (Ornoy et al. 1996, Street et al. 2008). Such factors make it difficult to define the primary effect of the agent under study and the secondary effects of the confounding factors. Most of the work in this area has been done in communities where crack cocaine is the most prevalent agent, but fewer long-term, well-conducted studies in heroin- and methadone-using mothers are available (Ornoy et al. 2001). However, it is now clear that the outcome is significantly affected by socioeconomic factors, and providing a nourishing family atmosphere can be protective against poor outcome (Singer et al. 2008).

Many people regard cannabis as a relatively benign drug of abuse and so less interest has been paid to the long-term effects on individuals regularly exposed in utero. Two large studies have now reported findings over a 20-year period showing clear if subtle long-term effects despite studying two widely differing client populations (Goldschmidt et al. 2000, Fried 2004). These data need to be interpreted in the light of changing patterns of cannabis use, with the development of more potent strains, which is likely to potentiate the effects

(Hardwick and King 2008, Hall and Degenhardt 2009). Other recreational drugs such as amphetamines and ecstasy are even more difficult to study, as use is intermittent and often mixed with other agents, making the effects difficult to quantify (Smith et al. 2006). Only one substantial long-term study of amphetamines is available (Eriksson et al. 2000).

Smoking is a common confounder in many of the studies of potential teratogenic factors in the use of drugs, alcohol and medications used in psychiatric conditions (Chapter 11). Combined with caffeine, it modulates its main effect through reduced birthweight (CARE Study Group 2008).

The different management strategies for these infants exposed to a range of potentially harmful teratogens do have many similarities (Section 3). Limitation of harm by reducing exposure prenatally, early intervention with parenting programmes, and specific management of comorbidities such as attention deficit disorder are important. However, this field is complicated by a range of factors including maternal acceptance of the possibility that the child's problems may be related to their drug taking, whether therapeutic, recreational or addictive, and consequent agreement to participate in programmes to support her in parenting postnatally (Williams-Petersen et al. 1994). The poor social circumstances of some of these families raises the need to protect the child from the risks of physical and emotional abuse and neglect. Social Care services have a duty to protect, but also to attempt to maintain children within their biological families, which is at times an impossible expectation to implement (Chapter 12). Even accommodation with other family members is fraught with difficulties in the midst of the complex relationship between a grandparent and their child whose infant has been exposed to teratogenic influences. It is possible to ameliorate the long-term effects with a combination of highly motivated experienced carers, specific targeted behavioural interventions (Advisory Council on the Misuse of Drugs 2003), and the judicious use of medication, particularly psychostimulants (Chapter 15). These individuals will, however, always remain vulnerable to a range of risks and impairments as they move on into adult life (Williams and Ross 2007).

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