Children of mothers with epilepsy exposed to antiepileptic drugs during pregnancy

Long-term neurocognitive and behavioral functioning from a family perspective

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General introduction

and outline of the thesis

General introduction

A few years ago, a mother with epilepsy stated in a Dutch newspaper '*Have I poisoned my child*?' During pregnancy, she had been using valproate, a commonly prescribed antiepileptic drug (AED)[1]. The placenta does not protect the unborn child against teratogens; environmental factors that can produce permanent abnormality in structure or function, abnormal growth, or death of the embryo or fetus[2–4]. It is not the first time that a drug is identified as bearing teratogenic risks. A well-known example is thalidomide, known in the Netherlands as Softenon®, which caused severe birth defects in more than 10,000 children, between 1957 and 1962[5].

Teratogens can be classified into different categories: infections and infestations, maternal diseases with transplacental effects, radiation, prescription drugs, over-the-counter-drugs, nutrition, social drugs, and occupational and environmental exposures (Table 1). A very recently discovered infectious teratogen is the Zika virus causing a spectrum of central nervous system and other abnormalities including severe microcephaly due to a disruption of brain development[6,7].

Although the mechanisms of teratogens are varied, Wilson described in 1977 'six general principles of teratology'[8], which still form the basis for research on teratogenesis[9]: *"1. Susceptibility to teratogenesis depends on the genotype of the conceptus and the manner in which this interacts with environmental factors. 2. Susceptibility to teratogenic agents varies with the developmental stage at the time of exposure. 3. Teratogenic agents act in specific ways (mechanisms) on developing cells and tissues to initiate abnormal embryogenesis (pathogenesis). 4. The final manifestations of abnormal development are death, malformation, growth retardation, and functional disorder. 5. The access of adverse environmental influences to developing tissues depends on the nature of the influences (agent). 6. Manifestations of deviant development increase in degree as dosage increases from the no-effect to the totally lethal level."* [8]

As an implication of these principles, teratogens may cause different effects on the pregnancy, or embryo/fetus. Table 2 describes possible manifestations of teratogenicity. When studying outcome in exposed pregnancies different confounding factors should be considered that are related to the outcome measure. These can be factors related to maternal disease, maternal characteristics (e.g., age, social economic status[30]), paternal factors (e.g., selective partner choice[31,32]), pregnancy-related factors, environmental factors, genetic factors and interactions with exposure.

Table 1. *Categories× of human teratogens and examples*

Category	Teratogen	Main effect
Infections	Rubella virus	Cataracts/congenital glaucoma, hearing impairment, mental retardation[11,12]
	Listeria *monocytogenes*[10]	Spontaneous abortion, stillbirth, preterm delivery[13]
	Zika virus	Microcephaly[6,7]
Infestations	Toxoplasmosis	Miscarriage, stillbirth, birth defects, cerebral calcifications, retinopathy[14]
Maternal disease	Diabetes mellitus	Congenital malformation, e.g. caudal regression syndrome[16], abnormal growth patterns[17]
Radiation (diagnostic, therapeutic, accidental)	Systemic lupus erythematosus, SLE[15]	Congenital heart block, spontaneous abortion, stillbirth, neonatal death, intrauterine growth retardation[15,18]
	Ionizing radiation	Microcephaly[14]
Prescription drugs	Thalidomide	Phocomelia[5]
	Antiepileptic drugs	Cleft lip/palate, heart defects, spina bifida, mental retardation, fetal AED syndromes[19–21]
Over-the-counter-drugs	Vitamin A & congeners	Retinoic acid embryopathy
	Paracetamol	Generally assumed to be safe, however studies suggest increased risk of attention-deficit-hyperactivity-disorder (ADHD)[22]
	Antibiotics	Some show teratogenic risks and health care professionals should consider these when prescribing to pregnant and lactating women[23]
Nutrition	Vitamin A deficiency	Cranial-neural-crest birth defects[24]
	Folic acid deficiency	Neural tube defects[25]
Occupational[26]	Any here described and other exposures	
Social drugs	Alcohol	Microcephaly, lower IQ, fetal alcohol syndrome (FAS)[27]
	Nicotine	Pregnancy complications, fetal growth restriction, preterm delivery, behavioral problems such as ADHD[28]
Environmental[29]	Pollution / All above	

× Categories are not mutually exclusive

As a result, the use of AEDs in women with epilepsy of childbearing potential is of continuous concern[34–36]. Various AEDs have shown teratogenic risks, and increased rates of major congenital malformations have been reported in exposed children[19,20,31].

Over the last two decades, more attention has been paid also to long-term effects of prenatal AED exposure on child neurocognitive and behavioral development[21]. However, still more knowledge is needed, specifically on newer AEDs, the potential spectrum of developmental side-effects, and the role of factors modifying the teratogenic risks

Table 2. *Different endpoints of teratogenicity*

Manifestations of teratogenesis	Examples
Reduced fertility	
Pregnancy complications	Miscarriage, stillbirth, preterm delivery
Fetal growth abnormality	Reduced or excessive growth / abnormal growth patterns
Perinatal problems	Functional maladaptation
Major malformations	Cleft lip/palate, heart defects, neural tube defects
Minor anomalies / dysmorphic features	Size or shape of head, ears (low-set), eyes (telecanthus), mouth (thin upper lip), chin (micrognathism), hands (single transverse palmar crease, reduction defects)
Malignancies	Vaginal carcinoma in DES daughters
Cognitive deficits	Intellectual disability, developmental delay
Behavioral problems	Autism spectrum disorder, ADHD
Third generation effects	Fertility problems in DES daughters[33]

DES = diethylstilbestrol

and eventual outcome, in order to help women and their treating physicians to make a well-informed choice on medication use during pregnancy[36,21,37–39].

The present dissertation focuses on the long-term effects of prenatal exposure to AED monotherapy on child developmental and behavioral outcomes, and, in addition, investigates the contribution to the child's development of having a mother with epilepsy, a chronic medical condition. Parent and parenting characteristics of mothers with epilepsy are examined from a family perspective, to give more insight in family factors that may be involved in child development.

Epilepsy is one of the most common neurological disorders worldwide, with an estimated prevalence between 0.4 and 1.0% of the population[40]. In the Netherlands, epilepsy concerns more than 180,000 people, of whom less than half are women[41]. Epilepsy is characterized by seizures[42,43], which are mainly treated with AEDs. About a third of people receiving AEDs are women of childbearing age[44]. Women with epilepsy who (want to) become pregnant have to make a difficult decision. It is believed that seizures can cause harm to the mother and the fetus that is greater than the potential adverse effects of medications on the embryonic development during pregnancy[45]. The majority of women with epilepsy is therefore recommended to continue using AEDs during pregnancy[39,46]. About 0.4% of all newborns have been exposed to AEDs during pregnancy[47,48].

Although most children are born apparently healthy, we know that the use of AEDs increases the risk of birth defects in the child[20,49]. Already since the late 60s, associations

have been found between prenatal exposure to AEDs and congenital malformations[50,51]. In the past years, international pregnancy registers have acquired more knowledge about the risks of different AEDs in monotherapy and at different dosages[20,35,52,53]. The European Registry of Antiepileptic Drugs and Pregnancy (EURAP) is one of these ongoing international prospective evaluation studies, aimed at studying the comparative safety of various AEDs used in pregnancy. The main outcome measure of EURAP is the presence or absence of structural birth defects in the child[54,55]. In the Netherlands, UMC Utrecht has coordinated EURAP Benelux from 2002 till 2013. Thereafter, the EURAP-NL database was moved to the Netherlands pharmacovigilance center Lareb where it currently is integrated into pREGnant[56]. Till now, EURAP-NL has registered over 1,000 pregnancies with maternal AED use, the vast majority for maternal epilepsy.

There are several types of AEDs, the most commonly used are valproate, carbamazepine, lamotrigine and levetiracetam[20], which are the subject of the present thesis. AEDs taken by the mother enter the bloodstream of the unborn child readily through the placenta[3]. The level of teratogenic risk is dependent on the type of AED, its dose, the timing of exposure, co-medication, and supposedly pharmacogenetic factors of both the mother and the embryofetus as well as the pharmacodynamic genetic make-up of the embryofetus[19,21]. The pathogenetic mechanisms of AED teratogenesis has been subject of a large number of experimental in vivo and in vitro studies, but failed to identify a unique mechanism for each of the AEDs involved or each of the type of abnormal outcome associated with each exposure. Multiple different mechanisms and interacting factors probably play a role[37,57–60] (Table 3).

Early case reports, retrospective studies and more recent prospective studies have documented developmental delay, learning disabilities, and lower IQ in children prenatally exposed to AEDs, especially those exposed to valproate[21,62]. A summary of studies on long-term neurocognitive and behavioral functioning after prenatal exposure to AEDs is given in Chapter 1. Most knowledge is obtained about valproate[62–102], while only a few studies have investigated the newer AEDs such as levetiracetam[82,93,97,99].

Table 3. *Examples of proposed mechanisms of teratogenesis*

Folate deficiency[61]
Abnormal neuronal migration
Decreased proliferation
AED-induced apoptosis
Altered synaptogenesis
Genetic modification / epigenetic

Teratogenic effects of AEDs show a wide spectrum of severity. At the one end of the spectrum, teratogenic effects may be incompatible with life or may lead to major physical defects and malformations, such as cleft lip/palate, heart defects, hypospadias and neural tube defects. They may also lead to intellectual disability. At the milder end of the spectrum, minor anomalies, specific cognitive and behavioral developmental problems may be found[62]. While earlier studies have focused mainly on the more severe physical consequences of *in utero* exposure to AEDs[19,47,103], in the last two decades studies of pregnancy outcome have broadened to include the "milder" cognitive and behavioral problems[38,58]. In reality, mild cognitive problems may not always be particularly mild and may be associated with chronic learning problems, and need for special educational support[21]. Likewise, the behavioral problems may require special guidance pertaining to child rearing and parenting methods while taking account of possible interference with maternal epilepsy and family background[104].

There is little knowledge regarding how mothers with epilepsy experience the upbringing of their child, whether they feel competent to take proper care of their children, whether they experience parenting stress, and whether they have sufficient social support. As children grow up, family factors may weaken or strengthen child development[105], independently or in interaction with the maternal condition, its treatment, and the genetic and teratogenic make-up of the child. Family factors and parenting are also important as, together with AED exposure, they could exacerbate preexisting developmental problems. Compared to control groups, families with a child with epilepsy had fewer positive family factors (e.g., they had lower parent-child relationship quality and more parental depression), which was associated with more behavioral problems in children[106,107]. *In utero* exposure to AEDs can be considered a risk factor for child development, but parenting and other family factors may have additional influence. This influence can be positive or negative: family factors may act as a risk factor for or may act as a buffer against developmental problems in children[108,109]. Given an established risk of AED exposure during the prenatal and the lactational period, more knowledge about parenting as an additional risk or protective factor in the development of children could help fine tune the parental guidance of these children.

Having a mother with a chronic medical condition affects not only the child but also the whole family[110]. Literature about parental epilepsy in relation to family functioning and parenting is scarce; existing literature on chronically ill parents focuses on diseases such as cancer, stroke, MS, HIV/AIDS or mixed populations[111]. These studies suggest that children with a parent with a chronic medical condition are more likely to have

behavioral problems, especially internalizing problem behavior[111]. Several studies conclude that behavioral problems in children of parents with a chronic condition are determined by the number of daily hassles and the perception of stress rather than by the severity of the illness[112,113].

It is generally assumed that a chronic condition is accompanied by functional impairment including mobility limitations and dependence in activities of daily living[111]. Epilepsy can be controlled with medication, but it still requires adherence to various life style rules. The impact of the condition may therefore not only be experienced by the mother with epilepsy, but also by those around her. Partners and children are also exposed to the various psychological, economic, and social stressors which may accompany the condition[114–116]. For example, worries about the health of the parent and about becoming ill themselves are widespread among children with a parent with a chronic condition[113]. Comorbid disorders may also affect parental and family functioning, and women with epilepsy have a higher risk of comorbid psychiatric disorders, especially depression[117,118]. Parental depression is often accompanied by decreased emotional availability and may directly or indirectly affect parenting and the quality of family relationships[119], which may therefore impact child development. However, health care professionals usually pay attention to the ill parent and spouse, and less so to their child(ren)[111].

There are various theoretical models which describe the relationship between parental chronic illness and child adjustment. One such model is the Family Systems-Illness (FSI) model[120], which explains a child's stress level based on the type of illness of the parent, and individual, family and illness life cycles. The type of illness is determined by the presence or absence of physical disability, the onset (acute or gradual), the course of the illness (progressive, episodic, or constant), the stage of the illness (crisis, chronic, or terminal) and by whether or not the illness is fatal[120]. Family life cycles are characterized by life events (e.g., marriage, birth of first child, adolescence, children leaving home) which mark the transition from one phase to the next. Keeping family life running requires a constant balance of the needs and abilities of family members. Individual and family factors which reestablish the family balance are beliefs and family communication, including marital state and parent-child communication[120].

Another model to examine child and family adaptation in relation to different family factors is the ABCX model of stress and coping[121,122]. This model states that stress and adaptation (X) results from family stressors and demands (A), family resources and strengths (B), and coping behaviors (C)[122]. In Chapter 2 we combined elements of

the FSI model with the ABCX model into a model of stress and coping with maternal epilepsy and family factors. Based on the ABCX model, maternal epilepsy and the possible teratogenic effects of *in utero* exposure to AEDs can be seen as stressors, while parenting and family factors can contribute to resilience. If parenting is less optimal it would then function as a risk factor. Based on the ABCX model, it can be assumed that if a parent has a chronic medical condition, the child may experience more stress, which may have impact on child development. It is therefore important to consider parenting stress, parental mental health, parenting and family functioning as mediating factors between earlier fetal exposure of the child, the current epilepsy of the mother and child developmental outcomes. Thus, the ABCX model helps to relate family factors and child development to each other[106].

To examine distinct family factors in children of mothers with epilepsy we followed the socio-ecological model of Bronfenbrenner[123] and the transactional model of Belsky[124]. With these models four types of family factors are distinguished, based on their proximity to the child: proximal, distal, contextual and global family factors[108,109]. Chapter 6 gives a more comprehensive description of these distinct family factors and how we examined family factors within this thesis.

Over the past years, several guidelines on epilepsy and pregnancy have appeared[39,125–127]. In 2018 the European Medicines Agency (EMA) came with a new guideline, which advised to avoid valproate in girls and women of childbearing potential where possible[128]. In addition, research has paid special attention to maternal wellbeing before, during and shortly after pregnancy[129–135]. These studies focus on how women with epilepsy experience the pregnancy, how they rate their quality of life and what their information needs are around epilepsy and pregnancy. There are however few studies on motherhood with epilepsy[136]. Timely and personal guidance for women with epilepsy who want to become pregnant is essential[137]. Having a child is more than being pregnant though and continued attention is needed for the welfare of mothers with school-aged children. Guidelines about maternal epilepsy, pregnancy, and parenting provide practical recommendations on the need for the infant to grow up in a safe home environment[138,139], but family factors such as parenting skills, parental psychopathology, parenting stress and the impact of maternal epilepsy on the child should not be overlooked.

This thesis contributes to more information on neurocognitive profiles of prenatally exposed children of mothers with epilepsy, including those exposed to the newer AEDs: lamotrigine and levetiracetam. It provides information on the behavioral development

of exposed children, with a screening of child psychiatric disorders, including autism. Moreover, this dissertation provides information on the influence of family factors in families with a mother with epilepsy, a domain that has rarely been studied.

Outline of the thesis

The central aim of this thesis is to obtain more knowledge about the long-term effects of prenatal exposure to AEDs on the neurocognitive and behavioral development of school-aged children. The nature and severity of neurocognitive and behavioral problems will be examined in relation to prenatal exposure and possible effects of AED dose. The contribution of distinct family factors in families with a mother with epilepsy, a chronic medical condition, is also investigated, including the wellbeing of mothers with epilepsy. With this thesis we hope to provide more information to future women with epilepsy who are or want to become pregnant and to provide starting points for treatment and support of children who have been exposed to AEDs during pregnancy and their families.

Chapter 1 describes the study protocol of the central research project EURAP & Development. It provides an overview of studies on long-term neurocognitive and behavioral functioning after prenatal exposure, and gives a comprehensive description of the study procedures and methods of the Dutch EURAP & Development study.

Chapter 2 presents a new perspective on the possible influence of family factors in the development of children of mothers with epilepsy. It consists of a literature review pertaining prenatal AED exposure and associations between child development and distinct family factors.

Subsequent chapters describe the various outcome measures of the Dutch EURAP & Development study. This concerns results from the first measurement when the children were six or seven years old, with consecutive focus on neurocognitive functioning (Chapter 3), behavioral development (Chapter 4), and specifically the risk of autism in prenatal exposed children (Chapter 5). Chapter 6 examines the mediating role of family factors in the relationship between maternal epilepsy and child behavior problems. Lastly, Chapter 7 gives a description of the mothers who participated in the study, and examines the wellbeing of mothers with epilepsy. The dissertation ends with a general discussion, which gives a reflection on the overall results, strengths and limitations of the study, possible future directions and clinical implications.

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