



## UvA-DARE (Digital Academic Repository)

### Exposure to antiepileptic drugs in pregnancy

*The need for a family factor framework*

Huber-Mollema, Y.; van Iterson, L.; Sander, J.W.; Oort, F.J.; Lindhout, D.; Rodenburg, R.

#### DOI

[10.1016/j.yebeh.2018.06.043](https://doi.org/10.1016/j.yebeh.2018.06.043)

#### Publication date

2018

#### Document Version

Final published version

#### Published in

Epilepsy and Behavior

[Link to publication](#)

#### Citation for published version (APA):

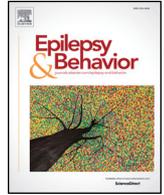
Huber-Mollema, Y., van Iterson, L., Sander, J. W., Oort, F. J., Lindhout, D., & Rodenburg, R. (2018). Exposure to antiepileptic drugs in pregnancy: The need for a family factor framework. *Epilepsy and Behavior*, *86*, 187-192. <https://doi.org/10.1016/j.yebeh.2018.06.043>

#### General rights

It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

#### Disclaimer/Complaints regulations

If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: <https://uba.uva.nl/en/contact>, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.



## Review

# Exposure to antiepileptic drugs in pregnancy: The need for a family factor framework



Yfke Huber-Mollema<sup>a,b</sup>, Loretta van Iterson<sup>a</sup>, Josemir W. Sander<sup>a,c,d</sup>, Frans J. Oort<sup>b</sup>, Dick Lindhout<sup>a,e</sup>, Roos Rodenburg<sup>a,b,\*</sup>

<sup>a</sup> Stichting Epilepsie Instellingen Nederland (SEIN), Heemstede, the Netherlands

<sup>b</sup> Research Institute of Child Development and Education, University of Amsterdam, the Netherlands

<sup>c</sup> NIHR University College London Hospitals, Biomedical Research Centre, UCL Institute of Neurology, Queen Square, London WC1N 3BG, UK

<sup>d</sup> Chalfont Centre for Epilepsy, Chalfont St Peter, UK

<sup>e</sup> Department of Genetics, University Medical Center Utrecht, the Netherlands

## ARTICLE INFO

## Article history:

Received 11 May 2018

Revised 20 June 2018

Accepted 21 June 2018

Available online 17 July 2018

## Keywords:

Maternal epilepsy  
Antiepileptic drugs  
Pregnancy  
Exposure  
Development  
Family factors

## ABSTRACT

**Purpose:** Children exposed to antiepileptic drugs (AEDs) in utero are at risk for developmental problems. Maternal epilepsy, its impact on the family system, and other family factors may also contribute. We reviewed the possible associations between family factors and developmental outcome in children who had been exposed to AED during pregnancy.

**Methods:** We conducted a narrative review and searched MEDLINE, Embase, Google Scholar, and PsycINFO on the following terms: in utero exposure, pregnancy outcome, and AEDs. A family factor framework (the ABCX model) served as the basis to review distinct family factors in children who were exposed to AEDs in pregnancy.

**Results:** Few studies have investigated these factors. Mothers with epilepsy have problems caring for themselves and for the child and experience more parenting stress. There is a paucity of studies of the possible impact of family factors on the neurocognitive and behavioral development of children of mothers with epilepsy.

**Discussion:** Further work is required to ascertain which family factors are associated with child development in addition to the effects of AED exposure and their potential interaction. As epilepsy may have considerable impact on intrafamily factors and as children are especially vulnerable to such effects, study designs incorporating family factors should be encouraged.

© 2018 Published by Elsevier Inc.

## 1. Introduction

Children of women with epilepsy exposed to antiepileptic drugs (AEDs) during pregnancy bear multiple risks. Being raised by a parent with a chronic medical condition as well as the possible teratogenic effects of prenatal exposure to AEDs may significantly contribute to the child's developmental outcomes. Knowledge is growing about the long-term effects of prenatal exposure to AEDs on neurocognitive and behavioral development [1–3], but less is known about the effects of family factors such as parenting skills or the impact of maternal epilepsy on the family [4,5]. It is germane to account for the impact of family factors on child development when assessing the long-term outcome of children exposed in utero to AEDs [6–12]. We conducted an exploratory narrative review on AED exposure during pregnancy and the associations between family factors and child developmental outcomes to

improve understanding of which family factors play a role in the development of children exposed to AEDs in utero.

## 2. Methods

### 2.1. Family factor framework: the ABCX model

We applied the ABCX model (Fig. 1) as a framework to categorize distinct family factors [13]. The ABCX model, based on stress and coping theory [14], states that stress and adaptation (X) results from family stressors and demands (A), family resources and strengths (B), and coping behaviors (C) [15]. Coping processes are essential in shaping reactions to stress and are influenced by environmental and individual variables [16]. Stress and coping are thus interrelated in an ongoing process that balances demands and available resources [13]. Maternal epilepsy and the possible teratogenic effects of AED exposure can be seen as stressors while parenting and family factors contribute to resilience.

\* Corresponding author at: University of Amsterdam, Postbus 15776, 1001 NG Amsterdam, the Netherlands.

E-mail address: [H.R.Rodenburg@uva.nl](mailto:H.R.Rodenburg@uva.nl) (R. Rodenburg).

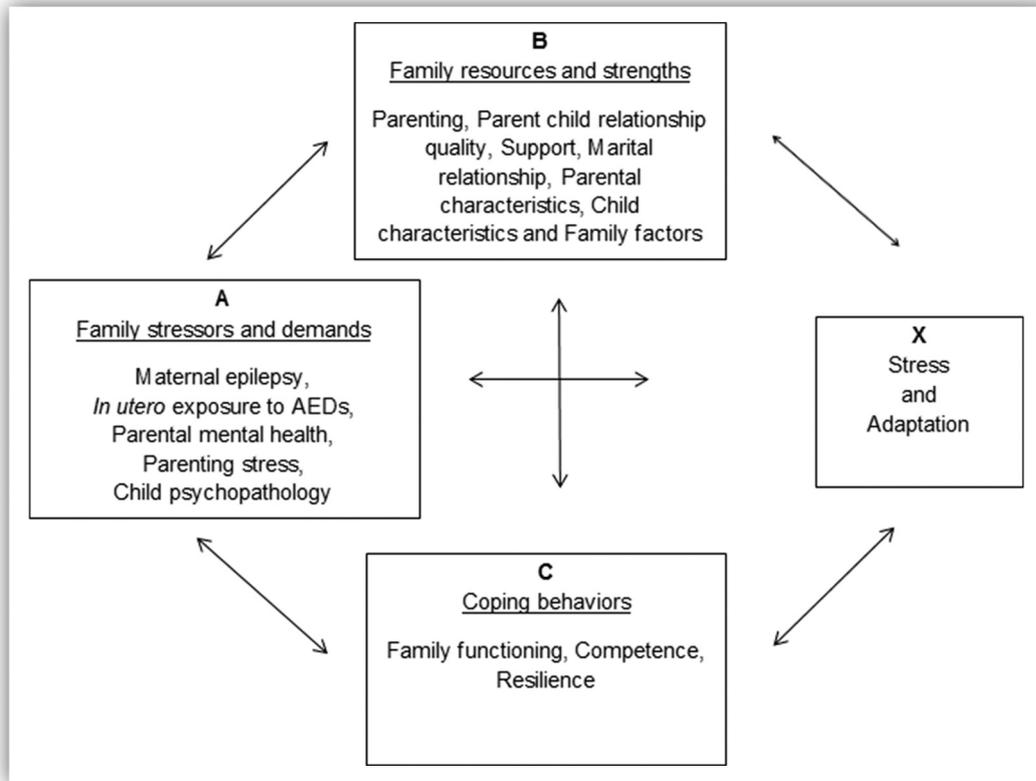


Fig. 1. Exposure to AEDs in pregnancy: ABCX model of stress and coping with maternal epilepsy and family factors.

## 2.2. Selection of studies

We searched the following databases: MEDLINE, Embase, Google Scholar, and PsycINFO. Other sources were trial registers and reference lists of eligible studies and review articles. The following terms were searched: in utero exposure, pregnancy outcome, and AEDs. Only human studies were searched. No language restrictions were made. The search strategy was designed by YH and RR, helped by two librarians. The full search strategy is available in [Appendix 1](#). Titles and abstracts of the articles found were screened and selected based on the following criteria.

## 2.3. Inclusion criteria

1. Studies including children (0–18 years) of mothers with epilepsy prenatally exposed to AEDs (monotherapy or polytherapy) or through breastfeeding, AND
2. Studies reporting on the associations between family factors (e.g., parenting stress, child-rearing practices) and child development in families with a mother with epilepsy, AND
3. Studies including the following control groups: children of mothers without epilepsy, children of mothers with epilepsy not taking AEDs during pregnancy, or children of mothers with epilepsy taking

**Table 1**  
Selected studies of family factors and parenting.

	Study authors	Publication year	Country	Sample size	Design	Research domain	Measure
1	Bagshaw, Crawford, and Chappell	2008	UK	84 mothers with epilepsy	Survey	Problems that mothers' with epilepsy experience when caring for their children	Questionnaire
2	Saramma, Sarma, and Thomas	2011	India	100 women with epilepsy and 93 women without epilepsy	Observational	Child-rearing knowledge and practice	Child-rearing knowledge and practice scale
3	Saramma, Sarma, and Thomas	2014	India	88 women with epilepsy	Experimental	Child-rearing knowledge and practice	Child-rearing knowledge and practice scale
4	Vinten et al.	2009	UK	242 children of mothers with epilepsy: 162 exposed and 80 nonexposed	Retrospective	Parenting stress	Parenting Stress Index
5	Cohen et al.	2011	North America/UK	229 exposed children of mothers with epilepsy	Prospective	Parenting stress	Parenting Stress Index
6	Cohen et al.	2013	North America/UK	195 exposed children of mothers with epilepsy	Prospective	Parenting stress	Parenting Stress Index
7	Titze et al.	2008	Germany	67 children of mothers with epilepsy (54 exposed and 13 nonexposed) and 49 control children	Prospective	Family environment	Home Observation for the Measurement of the Environment inventory

AED monotherapy who were compared with children exposed to other AED monotherapies.

### 3. Results

#### 3.1. Study characteristics

The search was conducted in July 2014 and repeated in April 2017. Seven studies were included (Table 1): a questionnaire survey [4]; five observational studies, focusing on mothers with epilepsy [17] or child developmental outcome [18–21]; and an experimental study on child-rearing [22].

#### 3.2. Family stressors and demands (A)

A few studies examined parenting stress in relation with behavior of preschool and school-aged children [18–20]. A retrospective study found an association between valproate exposure and high levels of parental stress induced by the child's maladaptive behavior (e.g., constant crying and frequent demand for help and attention, inability to adapt to changes in routine, overactivity, restlessness and short attention span, and being unhappy or depressed) [18]. Two prospective studies did not find significant differences between parents from children exposed to four commonly used AEDs on the Parenting Stress Index at three and six years of age [19,20].

#### 3.3. Family resources and strengths (B)

Some studies examined child-rearing knowledge and practices [4,17,22]. An online UK survey on the risks of caring for the baby and information provision on fulfilling the caring role reported that mothers with epilepsy experience problems with baby care [4]. From a list of common childcare activities (e.g., carrying/holding, ensuring safety, and feeding), caring outside the home and bathing were rated as being the most problematic whereas breastfeeding was much less problematic. Approximately 50% of the mothers had been provided with information about caring and managing risk during their pregnancy.

The knowledge and child-rearing skills were examined in two studies including women with and without epilepsy. Those with epilepsy had less knowledge and performed less well in all domains of child-rearing practices: feeding, growth and development, cleaning and protection, and infant stimulation [17]. Effects of a randomized study with a self-instructional module (SIM) during pregnancy on child-rearing knowledge and practice showed a significant increase in child-rearing knowledge three months postpartum [22]. The correlation did not reach statistical significance, but child-rearing knowledge appeared to be positively associated with child developmental outcome at one year of age. The developmental quotient (DQ) was higher in children whose mothers followed the SIM intervention than in children whose mothers received treatment as usual. Child-rearing practices of women did not significantly improve at three months postpartum [22]. In terms of resources and strengths, it can be derived from these studies that women with epilepsy have more a “lack of strengths” in child rearing practices and fewer child-rearing “resources”.

#### 3.4. Coping behaviors (C)

A long-term prospective German study used the HOME (Home Observation for the Measurement of the Environment) inventory to investigate quality and quantity of “family stimulation” in children of women with epilepsy [21]. Family stimulation was measured as access to sufficient toys and cultural experiences, maternal involvement, sensitivity with the child, and parental styles at two years of age. Children of mothers with and without epilepsy were followed from birth to adolescence. Differences in intelligence at adolescence were examined. A

comparison was made between children who were exposed to prenatal risks (presence or absence of AED exposure, seizures or nonoptimal obstetric conditions) and those who were exposed to family risks (poor or good quality of family environment). Children with prenatal risks appeared to be more vulnerable to environmental disadvantage (e.g., poor quality of parent–child relationship) than control children without prenatal risks are. In addition, children who had been cumulatively exposed to prenatal and family risks were found to have significantly lower intelligence quotients (IQs) in adolescence compared with children with only one or no risk factors [21].

### 4. Discussion

Thus far, research has focused predominantly on stressors and demands in mothers with epilepsy while less attention has been given to resiliency factors pertaining to family resources and strengths. The number of studies examining family factors in children is limited, but available studies suggest that mothers experience problems with parenting, including parenting stress. It is important though to consider a broader spectrum of family factors relating to child development and adaptation for children exposed to AEDs in utero and whose mothers have active epilepsy. That is, family factors may weaken or strengthen child development [23], independently or in interaction with the maternal condition, its treatment, and the genetic and teratogenic make-up of the child. For example, it is important to acknowledge the impact of active epilepsy on the child [6,7]. Difficulties associated with the mother's epilepsy, such as sleep deprivation, worries about taking care of the baby, or raising a child, may directly or indirectly contribute to the child's development [5,24–26]. Guidelines about maternal epilepsy, pregnancy, and parenting provide practical recommendations on the need for the child to grow up in a safe home environment [5,26], but family factors such as parenting skills should not be overlooked.

Mothers with epilepsy seem to experience specific problems with caring for the baby [4]. Possible associations between parenting and child development were not examined, however. Results suggest that only about half of the mothers received information about caring and epilepsy management during pregnancy. This is in line with a review into pregnancy-related knowledge and information needs, which concluded that more counseling for women with epilepsy is needed [27]. The relationship between child-rearing knowledge and practice and child developmental outcome at one year of age has been examined [22] but not with regard to long-term outcome. The SIM mainly focused on practical baby care in the first few months but not on parenting and development of the child later on in life. It is stated that epilepsy-related factors may influence child-rearing practice [17], but this was not further investigated. The importance of the family environment in early child development for long-term cognitive development was also shown when the child had prenatal risk of exposure to AEDs [21]. This study examined family environment at two years of age, but did not provide information about the contribution of *current* parenting at the time of child's assessment. As family and parenting factors can positively contribute to the development of the child [28], future studies may address relationships between caring, parenting, and child factors such as infant regulation. This may also hold for relationships between parenting and later child development.

In a retrospective study [18], high levels of parenting stress were associated with child maladaptive behavior. Another prospective study did not find differences between parents of children exposed to four commonly used AED types on parenting stress [19,20]. The levels of parenting stress, however, were not given. It therefore remains unclear whether the parents in this study experienced more stress than those from normative populations. It is known that parents of children from other special populations (e.g., with behavioral problems or with a chronic condition) experience more parenting stress [29,30]. As prenatal exposure to AEDs is a potential risk factor for child development, it is important to include parenting stress as this may add

cumulatively to child outcome. Causal relationships between parenting stress and child behavior should also be examined in the context of AED exposure and long-term child outcomes [31].

Thus, further studies are needed to assess the interrelationship between child development, exposure to AEDs during pregnancy, and the contribution of distinct family factors. Child developmental outcome should also be investigated in the context of active maternal epilepsy and its relation with *current* parenting, maternal mental health, and family functioning given the early exposure to AEDs in utero and the already established biological effects on the developing embryo and fetus. We recommend the use of specific measuring instruments for family factors and a measure to examine the impact of maternal epilepsy on the family and the child [32].

At present, we are conducting a study into children of mothers with epilepsy exposed in utero to AEDs, investigating the mediational role of family factors between child outcome at six or seven years of age and in two years' time at eight or nine years of age. Study procedures have been previously described [33]. As the burden of epilepsy may have considerable impact on family factors [34,35] and since children are especially vulnerable to these family factors [28], we encourage further studies in which distinct family factors are incorporated. This may shed light on the needs of families and may be used for the (development of) psychoeducational approaches or other interventions before, during, and following pregnancy [26,36]. Ultimately, this will contribute to enhance the quality of life of the child, the mother, and the whole family.

## Acknowledgments

RR has received a research grant from Stichting Panta Rhei for conducting the Dutch EURAP & Development study by YH. Stichting Panta Rhei was not involved in the study design, data collection, analysis and interpretation of the data, or manuscript preparation. JWS is based at NHHU University College London Hospitals/University College London Comprehensive Research Center, which receives a proportion of funding from the UK Department of Health's National Institute for Health Research Biomedical Research Centers funding scheme. He receives research support from the Dr. Marvin Weil Epilepsy Research Fund and the UK Epilepsy Society. Lastly, we would like to thank Janneke Staaks and Joost Daams of the University of Amsterdam for their assistance with the literature search and Dr. Gail S. Bell for reviewing the manuscript.

## Conflict of interest

YH, RR, Lvl, and FJO declare no conflict of interest. JWS has received research support from UCB and Eisai and personal honoraria for consulting and lecturing from UCB, Eisai, Bial, and Janssen–Cilag, which are involved in the manufacturing of AEDs. In the past (2000–2002), DL has received research grants from Janssen–Cilag, GlaxoSmithKline, Pfizer, and the Netherlands Epilepsy Foundation to start up the basic EURAP study in the Netherlands.

## Appendix 1. Search strategy: antiepileptic drugs and pregnancy

### Databases

Medline: 5.168 results (July 4, 2014)  
 PsycINFO: 862 results (July 4, 2014)  
 Embase: 5.692 results (July 1, 2014)  
 Total: 11.722 results  
 Total, deduplicated: 9.456 results  
 Google Scholar: 200 results were scanned, 62 results were selected (June 27, 2014)  
 Google Scholar: 1830 results (since 2013) (April 14, 2017)

## Medline

*Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)*

### #1 Pregnancy

pregnancy outcome/ OR maternal epilepsy.ti,ab. OR mothers with epilepsy.ti,ab. OR women with epilepsy.ti,ab. OR WWE.ti,ab. OR CME.ti,ab. OR teratogen\*.ti,ab. OR during pregnancy.ti,ab. OR prenatal exposure delayed effects/ OR maternal-fetal exchange/ OR ((pregnancy/ OR pregnan\*.ti,ab. OR prenatal\*.ti,ab. OR fetal.ti,ab. OR foetal.ti,ab. OR uter\*.ti,ab. OR antenatal\*.ti,ab. OR ante natal.ti,ab.) AND (expos\*.ti,ab. OR outcome\*.ti,ab. OR long term consequences.ti,ab. OR follow up.ti,ab. OR observation\*.ti,ab.)) OR breast feeding/ OR breastfeeding.ti,ab. OR breast feeding.ti,ab.

**Results: 300.524 (July 4, 2014)**

### #2 Antiepileptic drugs

exp. anticonvulsants/ OR anticonvuls\*.ti,ab. OR anti-convuls\*.ti,ab. OR anti-epilep\*.ti,ab. OR antiepilep\*.ti,ab. OR AED.ti,ab. OR AEDs.ti,ab. OR exp. epilepsy/ OR epilep\*.ti,ab. OR **Clonazepam/** OR Clonazepam.ti,ab. OR Klonopin.ti,ab. OR Naze.ti,ab. OR Rivotril.ti,ab. OR **Ethosuximide/** OR Ethosuximide\*.ti,ab. OR Emeside.ti,ab. OR Zarontin\*.ti,ab. OR **Felbama\*.ti,ab.** OR Felbatol.ti,ab. OR Taloxa.ti,ab. OR **Lacosamid\*.ti,ab.** OR Erlosamide.ti,ab. OR Vimpat.ti,ab. OR **Levetiracetam\*.ti,ab.** OR LEV.ti,ab. OR Keppra.ti,ab. OR **Oxcarbazepin\*.ti,ab.** OR Trileptal.ti,ab. OR **Phenobarbital/** OR Phenobarbit\*.ti,ab. OR Fenobarbit\*.ti,ab. OR Luminal.ti,ab. OR **Retigabin\*.ti,ab.** OR **Rufinamid\*.ti,ab.** OR **Primidone/** OR Primidon\*.ti,ab. OR Liskantint.ti,ab. OR Mylepsinum.ti,ab. OR Mysoline.ti,ab. OR Prysoline.ti,ab. OR Sertan.ti,ab. OR **Vigabatrin/** OR Vigabatrin\*.ti,ab. OR Sabril.ti,ab. OR **Zonisamid\*.ti,ab.** OR **Acetazolamide/** OR Acetazolamid\*.ti,ab. OR Diamox.ti,ab. OR **Carbamazepine/** OR Carbamazepin\*.ti,ab. OR CBZ.ti,ab. OR Equetro.ti,ab. OR Tegretol.ti,ab. OR **Clobazam.ti,ab.** OR Frisium.ti,ab. OR Onfi.ti,ab. OR **Ezogabin\*.ti,ab.** OR **Gabapentin.ti,ab.** OR Gabarone.ti,ab. OR Gabrion.ti,ab. OR Gralise.ti,ab. OR Neurontin.ti,ab. OR **Hydantoins/** OR Hydantoin\*.ti,ab. OR **Lamotrigin\*.ti,ab.** OR LTG.ti,ab. OR Lamitor.ti,ab. OR Lamictal.ti,ab. OR Lamotragin\*.ti,ab. OR **Nitrazepam/** OR Nitrazepam\*.ti,ab. OR Arem.ti,ab. OR Mogadon\*.ti,ab. OR **Phenytoin/** OR Phenytoin\*.ti,ab. OR PHT.ti,ab. OR Dilantin.ti,ab. OR Diphantoin\*.ti,ab. OR Diphenylhydantoin.ti,ab. OR Epanutin.ti,ab. OR Eptoin.ti,ab. OR Fenytoin\*.ti,ab. OR Phenytek.ti,ab. OR **Sulthiam\*.ti,ab.** OR **Pregabalin\*.ti,ab.** OR Lyrica.ti,ab. OR **Tiagabin\*.ti,ab.** OR Gabitril.ti,ab. OR **Topirama\*.ti,ab.** OR Topamax.ti,ab. OR **Valproic acid/** OR Valproic.ti,ab. OR VPA.ti,ab. OR Convulex.ti,ab. OR Depakin\*.ti,ab. OR Depakote.ti,ab. OR Epilim.ti,ab. OR Orfiril.ti,ab. OR Stavzor.ti,ab. OR Valparin.ti,ab. OR Valpro.ti,ab. OR Valproat\*.ti,ab. OR Vilapro.ti,ab.

**Results: 298.936 (July 4, 2014)**

### #3 Animals

animal/ NOT human/

### #4 Trials and research teams

NCT01730170.af. OR NCT00021866.af. OR NCT01097720.af. OR NCT00353886.af. OR NCT00345475.af. OR NEAD study group.au. OR MONEAD.ti,ab. OR RNEAD.ti,ab. OR LMNDG.ti,ab,au. OR "Liverpool and Manchester Neurodevelopment\*"ti,ab,au.

**Results: 19 (June 23, 2014)**

1 AND 2: 7.189 results (July 4, 2014)

NOT 3: 5.167 results (July 4, 2014)

OR 4: 5.168 results (July 4, 2014)

## PsycINFO

*OvidSP*

### #1 Pregnancy

pregnancy/ OR pregnancy outcomes/ OR pregnan\*.ti,ab,id. OR maternal epilepsy.ti,ab,id. OR mothers with epilepsy.ti,ab,id. OR women with epilepsy.ti,ab,id. OR WWE.ti,ab,id. OR CME.ti,ab,id. OR prenatal exposure/ OR ((prenatal\* OR fetal OR foetal OR uter\* OR antenatal\* OR ante natal).ti,ab,id. AND (expos\* OR outcome\* OR long term consequences OR follow up).ti,ab,id.) OR teratogen\*.ti,ab,id. OR breast feeding/ OR breastfeeding.ti,ab,id. OR breast feeding.ti,ab,id. OR mothers/

**Results: 68.210 (July 4, 2014)****#2 Antiepileptic drugs**

exp. anticonvulsive drugs/ OR anticonvuls\*.ti,ab,id. OR anti-convuls\*.ti,ab,id. OR AED.ti,ab,id. OR AEDs.ti,ab,id. OR antiepilep\*.ti,ab,id. OR anti-epilep\*.ti,ab,id. OR epilepsy/ OR epileptic seizures/ OR epilep\*.ti,ab,id. OR Clonazepam/ OR Clonazepam.ti,ab,id. OR Klonopin.ti,ab,id. OR Naze.ti,ab,id. OR Rivotril.ti,ab,id. OR Ethosuximid\*.ti,ab,id. OR Emeside.ti,ab,id. OR Zaronin\*.ti,ab,id. OR Felbama\*.ti,ab,id. OR Felbatol.ti,ab,id. OR Taloxa.ti,ab,id. OR Lacosamid\*.ti,ab,id. OR Erlosamide.ti,ab,id. OR Vimpat.ti,ab,id. OR Levetiracetam\*.ti,ab,id. OR LEV.ti,ab,id. OR Keppra.ti,ab,id. OR Oxcarbazepin\*.ti,ab,id. OR Trileptal.ti,ab,id. OR Phenobarbital/ OR Phenobarbit\*.ti,ab,id. OR Fenobarbit\*.ti,ab,id. OR Luminal.ti,ab,id. OR Retigabin\*.ti,ab,id. OR Rufinamid\*.ti,ab,id. OR Primidone/ OR Primidon\*.ti,ab,id. OR Liskantin.ti,ab,id. OR Mylepsinum.ti,ab,id. OR Mysoline.ti,ab,id. OR Prysoline.ti,ab,id. OR Sertan.ti,ab,id. OR Vigabatrin/ OR Vigabatrin\*.ti,ab,id. OR Sabril.ti,ab,id. OR Zonisamid\*.ti,ab,id. OR Acetazolamide/ OR Acetazolamid\*.ti,ab,id. OR Diamox.ti,ab,id. OR Carbamazepine/ OR Carbamazepin\*.ti,ab,id. OR CBZ.ti,ab,id. OR Equetro.ti,ab,id. OR Tegretol.ti,ab,id. OR Clobazam.ti,ab,id. OR Frisium.ti,ab,id. OR Onfi.ti,ab,id. OR Ezogabin\*.ti,ab,id. OR Gabapentin.ti,ab,id. OR Gabarone.ti,ab,id. OR Gabrion.ti,ab,id. OR Gralise.ti,ab,id. OR Neurontin.ti,ab,id. OR Hydantoin\*.ti,ab,id. OR Lamotrigin\*.ti,ab,id. OR LTG.ti,ab,id. OR Lamitor.ti,ab,id. OR Lamictal.ti,ab,id. OR Lamotragin\*.ti,ab,id. OR Nitrazepam/ OR Nitrazepam\*.ti,ab,id. OR Arem.ti,ab,id. OR Mogadon\*.ti,ab,id. OR Phenytoin\*.ti,ab,id. OR PHT.ti,ab,id. OR Dilantin.ti,ab,id. OR Diphantoin\*.ti,ab,id. OR Diphenylhydantoin/ OR Diphenylhydantoin.ti,ab,id. OR Epanutin.ti,ab,id. OR Eptoin.ti,ab,id. OR Fenytoin\*.ti,ab,id. OR Phenytek.ti,ab,id. OR Sulthiam\*.ti,ab,id. OR Pregabalin/ OR Pregabalin\*.ti,ab,id. OR Lyrica.ti,ab,id. OR Tiagabin\*.ti,ab,id. OR Gabitril.ti,ab,id. OR Topirama\*.ti,ab,id. OR Topamax.ti,ab,id. OR Valproic acid/ OR Valproic.ti,ab,id. OR VPA.ti,ab,id. OR Convulex.ti,ab,id. OR Depakin\*.ti,ab,id. OR Depakote.ti,ab,id. OR Epilim.ti,ab,id. OR Orfiril.ti,ab,id. OR Stavzor.ti,ab,id. OR Valparin.ti,ab,id. OR Valpro.ti,ab,id. OR Valproat\*.ti,ab,id. OR Vilapro.ti,ab,id.

**Results: 42.739 (July 4, 2014)****#3 Animal studies**

animal.po NOT human.po

**#4 Trials and research teams**

NCT01730170.af. OR NCT00021866.af. OR NCT01097720.af. OR NCT00353886.af. OR NCT00345475.af. OR NEAD.ti,ab,ca,gs. OR MONEAD.ti,ab,ca,gs. OR RNEAD.ti,ab,ca,gs. OR LMNDG.ti,ab,ca,gs. OR "Liverpool and Manchester Neurodevelopment\*".ti,ab,ca,gs.

**Results: 56 (July 4, 2014)**

1 AND 2: 1.081 results (July 4, 2014)

NOT 3: 827 results (July 4, 2014)

OR 4: 862 results (July 4, 2014)

**Embase**

OvidSP

**#1 Pregnancy**

pregnancy outcome/ OR maternal epilepsy.ti,ab,kw. OR mothers with epilepsy.ti,ab,kw. OR women with epilepsy.ti,ab,kw. OR WWE.ti,ab,kw. OR CME.ti,ab,kw. OR teratogen\*.ti,ab,kw,sh. OR during pregnancy.ti,ab,kw. OR prenatal exposure/ OR ((pregnancy/ OR pregnan\*.ti,ab,kw. OR prenatal\*.ti,ab,kw. OR fetal.ti,ab,kw. OR foetal.ti,ab,kw. OR uter\*.ti,ab,kw. OR antenatal\*.ti,ab,kw. OR ante natal\*.ti,ab,kw.) AND (exposure/ OR expos\*.ab,ti,kw. OR outcome\*.ab,ti,kw. OR long term consequences.ti,ab,kw. OR follow up.ti,ab,kw,sh. OR observation\*.ab,ti,kw,sh.)) OR breast feeding/ OR breastfeeding.ti,ab,kw. OR breast feeding.ti,ab,kw.

**#2 Antiepileptic drugs**

(Clonazepam.ti,ab,kw,sh. OR Klonopin.ti,ab,kw. OR Naze.ti,ab,kw. OR Rivotril.ti,ab,kw. OR Ethosuximid\*.ti,ab,kw,sh. OR Emeside.ti,ab,kw. OR Zaronin\*.ti,ab,kw. OR Felbama\*.ti,ab,kw,sh. OR Felbatol.ti,ab,kw. OR Taloxa.ti,ab,kw. OR Lacosamid\*.ti,ab,kw,sh. OR Erlosamide.ti,ab,kw. OR Vimpat.ti,ab,kw. OR Levetiracetam\*.ti,ab,kw,sh. OR LEV.ti,ab,kw. OR Keppra.ti,ab,kw. OR Oxcarbazepin\*.ti,ab,kw,sh. OR Trileptal.ti,ab,kw.

OR Phenobarbit\*.ti,ab,kw,sh. OR Fenobarbit\*.ti,ab,kw. OR Luminal.ti,ab,kw. OR Retigabin\*.ti,ab,kw,sh. OR Rufinamid\*.ti,ab,kw,sh. OR Primidon\*.ti,ab,kw,sh. OR Liskantin.ti,ab,kw. OR Mylepsinum.ti,ab,kw. OR Mysoline.ti,ab,kw. OR Prysoline.ti,ab,kw. OR Sertan.ti,ab,kw. OR Vigabatrin\*.ti,ab,kw,sh. OR Sabril.ti,ab,kw. OR Zonisamid\*.ti,ab,kw,sh.) OR ((exp anticonvulsive agent/ OR anticonvuls\*.ti,ab,kw. OR anticonvuls\*.ti,ab,kw. OR anti-epilep\*.ti,ab,kw. OR antiepilep\*.ti,ab,kw. OR AED.ti,ab,kw. OR AEDs.ti,ab,kw. OR Acetazolamid\*.ti,ab,kw,sh. OR Diamox.ti,ab,kw. OR Carbamazepin\*.ti,ab,kw,sh. OR CBZ.ti,ab,kw. OR Equetro.ti,ab,kw. OR Tegretol.ti,ab,kw. OR Clobazam.ti,ab,kw,sh. OR Frisium.ti,ab,kw. OR Onfi.ti,ab,kw. OR Ezogabin\*.ti,ab,kw,sh. OR Gabapentin.ti,ab,kw,sh. OR Gabarone.ti,ab,kw. OR Gabrion.ti,ab,kw. OR Gralise.ti,ab,kw. OR Neurontin.ti,ab,kw. OR Hydantoin\*.ti,ab,kw,sh. OR Lamotrigin\*.ti,ab,kw,sh. OR LTG.ti,ab,kw. OR Lamitor.ti,ab,kw. OR Lamictal.ti,ab,kw. OR Lamotragin\*.ti,ab,kw. OR Nitrazepam\*.ti,ab,kw,sh. OR Arem.ti,ab,kw. OR Mogadon\*.ti,ab,kw. OR Phenytoin\*.ti,ab,kw,sh. OR PHT.ti,ab,kw. OR Dilantin.ti,ab,kw. OR Diphantoin\*.ti,ab,kw. OR Diphenylhydantoin.ti,ab,kw. OR Epanutin.ti,ab,kw. OR Eptoin.ti,ab,kw. OR Fenytoin\*.ti,ab,kw. OR Phenytek.ti,ab,kw. OR Sulthiam\*.ti,ab,kw,sh. OR Pregabalin\*.ti,ab,kw,sh. OR Lyrica.ti,ab,kw. OR Tiagabin\*.ti,ab,kw,sh. OR Gabitril.ti,ab,kw. OR Topirama\*.ti,ab,kw,sh. OR Topamax.ti,ab,kw. OR Valproic.ti,ab,kw,sh. OR VPA.ti,ab,kw. OR Convulex.ti,ab,kw. OR Depakin\*.ti,ab,kw. OR Depakote.ti,ab,kw. OR Epilim.ti,ab,kw. OR Orfiril.ti,ab,kw. OR Stavzor.ti,ab,kw. OR Valparin.ti,ab,kw. OR Valpro.ti,ab,kw. OR Valproat\*.ti,ab,kw. OR Vilapro.ti,ab,kw.) AND (exp epilepsy/ OR "seizure, epilepsy and convulsion"/ OR epilep\*.ti,ab,kw. OR antiepilep\*.ti,ab,kw. OR anti-epilep\*.ti,ab,kw. OR seizure/ OR seizure\*.ti,ab,kw. OR convulsion/ OR convuls\*.ti,ab,kw. OR epilepsy abstracts.ec.))

**#3 Animal studies**

NOT ((animal/ OR animal experiment/ OR animal model/ OR nonhuman/) NOT human/)

**#4 Trials and research teams**

NCT01730170.cn. OR NCT00021866.cn. OR NCT01097720.cn. OR NCT00353886.cn. OR NCT00345475.cn. OR NEAD.ti,ab,kw,cn. OR MONEAD.ti,ab,kw,cn. OR RNEAD.ti,ab,kw,cn. OR LMNDG.ti,ab,kw. OR "Liverpool and Manchester Neurodevelopment\*".ti,ab,kw.

**((1 AND 2) NOT 3) OR 4: 5.692 results (July 1, 2014)****Google Scholar**

("maternal epilepsy" | "mothers with epilepsy" | "prenatal exposure" | breastfeeding) (antiepileptics | anti-epileptics | anticonvulsants | anti-convulsants)

NCT01730170 | NCT00021866 | NCT01097720 | NCT00353886 | NCT00345475 | "NEAD study group" | MONEAD | RNEAD | LMNDG | "Liverpool and Manchester Neurodevelopment"

or

((("maternal epilepsy" | "mothers with epilepsy" | "prenatal exposure") (antiepileptics | anticonvulsants)) | (NCT00021866 | NCT00345475 | "NEAD study" | "Liverpool and Manchester Neurodevelopment"))

**References**

- [1] Bromley R, Weston J, Adab N, Greenhalgh J, Sanniti A, McKay AJ, et al. Treatment for epilepsy in pregnancy: neurodevelopmental outcomes in the child. *Cochrane Database Syst Rev* 2014. <https://doi.org/10.1002/14651858.CD010236.pub2>.
- [2] Gerard E, Meador K. An update on maternal use of antiepileptic medications in pregnancy and neurodevelopment outcomes. *J Pediatr Genet* 2015;04:094–110. <https://doi.org/10.1055/s-0035-1556741>.
- [3] Bromley RL, Baker GA. Fetal antiepileptic drug exposure and cognitive outcomes. *Seizure* 2017;44:225–31. <https://doi.org/10.1016/j.seizure.2016.10.006>.
- [4] Bagshaw J, Crawford P, Chappell B. Problems that mothers' with epilepsy experience when caring for their children. *Seizure* 2008;17:42–8. <https://doi.org/10.1016/j.seizure.2007.06.004>.
- [5] Cabral-Lim LI. Delivery, breast feeding and child-rearing in women with epilepsy. *Neurol Asia* 2013;18:31–4.
- [6] Sieh DS. The impact of parents' chronic medical condition on children; 2012 (Doctoral dissertation, University of Amsterdam, The Netherlands) Retrieved from [https://pure.uva.nl/ws/files/1766529/110418\\_17.pdf](https://pure.uva.nl/ws/files/1766529/110418_17.pdf).
- [7] Rolland JS. Parental illness and disability: a family systems framework. *J Fam Ther* 1999;21:242–66.

- [8] Visser-Meily J, Meijer A. Stroke, consequences for the family and recommendations for rehabilitation. *Parent Child Relat New Res* 2006;157–74.
- [9] Korneluk YG, Lee CM. Children's adjustment to parental physical illness. *Clin Child Fam Psychol Rev* 1998;1:179–93.
- [10] Dufour MJ, Meijer AM, van de Port I, Visser-Meily JMA. Moeilijke momenten en stress bij kinderen van chronisch zieke ouders. *Neth J Psychol* 2006;61:51–60. <https://doi.org/10.1007/BF03062361>.
- [11] Armistead L, Klein K, Forehand R. Parental physical illness and child functioning. *Clin Psychol Rev* 1995;15:409–22.
- [12] Beghi E, Roncolato M, Visona G. Depression and altered quality of life in women with epilepsy of childbearing age. *Epilepsia* 2004;45:64–70.
- [13] Rodenburg R, Meijer AM, Deković M, Aldenkamp AP. Parents of children with enduring epilepsy: predictors of parenting stress and parenting. *Epilepsy Behav* 2007;11:197–207. <https://doi.org/10.1016/j.yebeh.2007.05.001>.
- [14] Lazarus RS. Stress, appraisal, and coping. New York: Springer; 1984.
- [15] Patterson J, McCubbin H. Family stress and adaptation to crises: a double ABCX model of family behavior. *Fam Stud Rev Yearb* 1983;125–35.
- [16] Lazarus RS. From psychological stress to the emotions: a history of changing outlooks. *Annu Rev Psychol* 1993;44:1–22.
- [17] Saramma PP, Sarma PS, Thomas SV. Women with epilepsy have poorer knowledge and skills in child-rearing than women without epilepsy. *Seizure* 2011;20:575–9. <https://doi.org/10.1016/j.seizure.2011.04.008>.
- [18] Vinten J, Bromley RL, Taylor J, Adab N, Kini U, Baker GA. The behavioral consequences of exposure to antiepileptic drugs in utero. *Epilepsy Behav* 2009;14:197–201. <https://doi.org/10.1016/j.yebeh.2008.10.011>.
- [19] Cohen MJ, Meador KJ, Browning N, Baker GA, Clayton-Smith J, Kalayjian LA, et al. Fetal antiepileptic drug exposure: motor, adaptive, and emotional/behavioral functioning at age 3 years. *Epilepsy Behav* 2011;22:240–6. <https://doi.org/10.1016/j.yebeh.2011.06.014>.
- [20] Cohen MJ, Meador KJ, Browning N, May R, Baker GA, Clayton-Smith J, et al. Fetal antiepileptic drug exposure: adaptive and emotional/behavioral functioning at age 6 years. *Epilepsy Behav* 2013;29:308–15. <https://doi.org/10.1016/j.yebeh.2013.08.001>.
- [21] Titze K, Koch S, Helge H, Lehmkuhl U, Rauh H, Steinhausen H-C. Prenatal and family risks of children born to mothers with epilepsy: effects on cognitive development. *Dev Med Child Neurol* 2008;50:117–22. <https://doi.org/10.1111/j.1469-8749.2007.02020.x>.
- [22] Saramma PP, Sarma PS, Thomas SV. Effect of a self-instructional module on the child-rearing knowledge and practice of women with epilepsy. *Seizure* 2014;23:424–8. <https://doi.org/10.1016/j.seizure.2014.02.006>.
- [23] Appleyard K, Egeland B, Dulmen MHM, Alan Sroufe L. When more is not better: the role of cumulative risk in child behavior outcomes. *J Child Psychol Psychiatry* 2005;46:235–45. <https://doi.org/10.1111/j.1469-7610.2004.00351.x>.
- [24] Galanti M, Jeffrey Newport D, Pennell PB, Titchner D, Newman M, Knight BT, et al. Postpartum depression in women with epilepsy: influence of antiepileptic drugs in a prospective study. *Epilepsy Behav* 2009;16:426–30. <https://doi.org/10.1016/j.yebeh.2009.07.009>.
- [25] Bjørk MH, Veiby G, Reiter SC, Berle JØ, Daltveit AK, Spigset O, et al. Depression and anxiety in women with epilepsy during pregnancy and after delivery: a prospective population-based cohort study on frequency, risk factors, medication, and prognosis. *Epilepsia* 2015;56:28–39. <https://doi.org/10.1111/epi.12884>.
- [26] Lannon SL. Epilepsy, pregnancy and parenting—an American perspective. *Seizure* 1994;3:85–93.
- [27] McGrath A, Sharpe L, Lah S, Parratt K. Pregnancy-related knowledge and information needs of women with epilepsy: a systematic review. *Epilepsy Behav* 2014;31:246–55. <https://doi.org/10.1016/j.yebeh.2013.09.044>.
- [28] Harvey B, Matte-Gagné C, Stack DM, Serbin LA, Ledingham JE, Schwartzman AE. Risk and protective factors for autonomy-supportive and controlling parenting in high-risk families. *J Appl Dev Psychol* 2016;43:18–28. <https://doi.org/10.1016/j.appdev.2015.12.004>.
- [29] Rodenburg R, Meijer AM, Deković M, Aldenkamp AP. Family factors and psychopathology in children with epilepsy: a literature review. *Epilepsy Behav* 2005;6:488–503. <https://doi.org/10.1016/j.yebeh.2005.03.006>.
- [30] Barroso NE, Mendez L, Graziano PA, Bagner DM. Parenting stress through the lens of different clinical groups: a systematic review & meta-analysis. *J Abnorm Child Psychol* 2017. <https://doi.org/10.1007/s10802-017-0313-6>.
- [31] Stone LL, Mares SHW, Otten R, Engels RCME, Janssens JMAM. The co-development of parenting stress and childhood internalizing and externalizing problems. *J Psychopathol Behav Assess* 2016;38:76–86. <https://doi.org/10.1007/s10862-015-9500-3>.
- [32] Camfield C, Breau L, Camfield P. Impact of pediatric epilepsy on the family: a new scale for clinical and research use. *Epilepsia* 2001;42:104–12.
- [33] Huber-Mollema Y, van Iterson L, Oort FJ, Lindhout D, Rodenburg R. EURAP & development: study protocol of a Dutch prospective observational study into fetal antiepileptic drug exposure and long term neurocognitive, behavioral and family outcomes. [psyarxiv.com/b8dyj](https://psyarxiv.com/b8dyj); 2018.
- [34] de Boer HM, Mula M, Sander JW. The global burden and stigma of epilepsy. *Epilepsy Behav* 2008;12:540–6. <https://doi.org/10.1016/j.yebeh.2007.12.019>.
- [35] Tedrus GMAS, Pereira RB, Zoppi M. Epilepsy, stigma, and family. *Epilepsy Behav* 2018;78:265–8. <https://doi.org/10.1016/j.yebeh.2017.08.007>.
- [36] Weckesser A, Denny E. Re-working biographies: women's narratives of pregnancy whilst living with epilepsy. *Soc Sci Med* 2017;185:110–7. <https://doi.org/10.1016/j.socscimed.2017.05.036>.