

The use of teratogenic medication during pregnancy and congenital anomalies of the offspring in the Northern Netherlands, 1981-2019

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Background

Medication use during pregnancy might be necessary, for example in patients with epilepsy. However, prescribed medications are not always safe during pregnancy. There are several classification systems for the safety of medication during pregnancy. Nowadays in Europe and the United States, descriptive text is used, instead of the formerly used letter classification A t/m D and X. For drugs that might lead to congenital anomalies in the offspring, the Dutch Teratology Information Service (TIS) uses:

1. Teratogen effect, outweigh benefit and risk, if necessary: monitor on adverse effects
2. Teratogen effect, do not use (temporarily)

For some of the medications in the second group, *teratogen effect, do not use (temporarily)*, a Pregnancy Prevention Program (PPP) has been set up.

Eurocat collects data since 1981 about possible risk factors for congenital anomalies. Parents fill in a questionnaire, which results in information about the use of medication by the mother during pregnancy, of the father during periconception, as well as information about chronic diseases, special health issues during pregnancy and lifestyle factors. Additional data about prescribed medications is collected from pharmacies. For this report we yearly investigate the Eurocat database to find out if and how many teratogenic medications were used by the mothers, and investigate which anomalies have occurred in the exposed offspring.

Method

From the Eurocat database, all cases born between 1981 and 2019 were selected. We identified all cases that were exposed in utero to a medication described with 'teratogen effect' according to the TIS classification, or having a Pregnancy Prevention Program (PPP).

Mothers who used medication from category 1 (table 1), category 2 (table 2), or with a PPP (table 3) were counted.

A mother could occur in more than one medication group. Frequency tables are given for medication use in every medication group. Cases exposed to medications used in the second or third trimester only from categories 1 and 2 were excluded. All exposures to medications with a PPP were counted.

The Fisher's exact test (two sided) was used for associations on the level of the main groups of congenital anomalies of the offspring and teratogenic medication of the mother (SPSS Statistics, version 23).

Associations with a p-value less than .05 were considered significant. Medications with a count less than 5 were excluded from the test. Cases with multiple congenital anomalies are counted for in more than one anomaly group.

Table 1. Medication from category 1: ‘Teratogen effect, outweigh benefit and risk, monitor on adverse effects’

Medication name	Group
Valproic acid*, carbamazepine, phenytoin, topiramate	Antiepileptics, other
Phenobarbital , primidone	Antiepileptics, barbiturate class
Carbimazole, propylthiouracil, thiamazole	Thyreostatics
Lithium	Bipolar disorder treatment

**additional advice TIS: ‘Try to avoid the use of Valproic acid in pregnancy’.*

Table 2. Medication from category 2: ‘ Teratogen effect, do not use (temporarily)’

Medication name	Group
(dihydro)ergotamine	Antimigraine
Acenocoumarol, warfarin, fenprocoumon	Anticoagulation
ACE-inhibitors	Cardiovascular treatment
ATII-antagonists	Cardiovascular treatment
Tetracycline antibacterials	Antibiotics
Aminoglycoside antibacterials	Antibiotics
Kinine	Antimalaria
Nandrolone	Anabolic steroid
Cyproterone, danazol, tamoxifen	Antihormones
Methotrexate	Antirheumatics
Fluorouracil	Cytostatics

Table 3. Medication with a Pregnancy Prevention Program

Medication name	Group
Isotretinoin	Antiacne
Acitretinoin	Antipsoriasis
Thalidomide	Antileprosy/antitumor
Lenalidomide, pomalidomide	Multiple myeloma
Alitretinoin	Severe eczema
Ambrisentan, bosentan, macitentan (*)	Pulmonary arterial hypertension
Vismodegib	Basal cell carcinoma
Mycofenolic acid	Immunosuppressant

() PPP due to maternal risks due to underlying illness*

Results

In the period 1981-2019, 18,345 cases are registered at Eurocat. We discarded cases with a known cause, for example chromosomal anomalies, and cases with no information about medication use, leaving 11,124 cases.

Medication of category 1 and 2 was counted 303 times in total. Medication with a PPP was counted only once. For each group we counted the following numbers (table 4).

**Table 4. Number of cases exposed to medication from category 1 and 2, or with a PPP
Eurocat database 1981-2019**

Medication name	N
Category 1	Total count 88
Valproic acid, Carbamazepine, Phenytoin, Topiramate, Phenobarbital, Primidone (all antiepileptics)	72*
<i>Valproic acid</i>	41
<i>Carbamazepine, Phenytoin, Topiramate</i>	31
<i>Phenobarbital, Primidone</i>	4
Carbimazole, Propylthiouracil, Thiamazole	10
Lithium	6
Category 2	Total count 215
Tetracycline antibacterials	181
Acenocoumarol, Warfarin, Fenprocoumon	18
(dihydro)Ergotamine	5
ACE-inhibitors	6
Methotrexate	1
Angiotensin II-antagonists	4
Aminoglycoside antibacterials	0
Kinine	0
Nandrolone	0
Cyproterone, Danazol, Tamoxifen	0
Fluorouracil	0
Pregnancy Prevention Program	Total count 1
Isotretinoin	1
Acitretinoin	0
Thalidomide	0
Lenalidomide, Pomalidomide	0
Alitretinoin	0
Ambrisentan, Bosentan, Macitentan	0
Vismodegib	0
Mycofenolic acid	0

*Some mothers used a barbiturate as well as another antiepileptic.

Congenital anomalies in the main groups were counted 12,304 times in total. For each main anomaly group we counted the following numbers (table 5).

Table 5. Main congenital anomaly groups, Eurocat database 1981-2019

Main anomaly group	N
	<i>Total count</i> 12,304
Anomalies of the nervous system	890
Eye anomalies	234
Ear anomalies	73
Congenital heart defects	2950
Congenital malformations of the respiratory system	256
Oro-facial clefts	998
Congenital malformations of the digestive system	1359
Genital anomalies	879
Congenital malformations of the urinary system	1327
Limb anomalies	3150
Abdominal wall defects	188

For each group of teratogenic medication, we compared exposed cases from a specific anomaly group with all other cases not exposed to this specific teratogenic medication. Total number of cases is 11,124. As mentioned before, a mother could occur in more than one medication group and cases with multiple congenital anomalies cover more than one anomaly group. The result of significant associations are shown in table 6.

Table 6. Number of Category 1 and 2 medication associated with specific main congenital anomaly groups, Eurocat database 1981-2019

	Anomalies of the nervous system		
Exposed to medication category 1 :			
	n	expected count	p-value
Valproic acid, Carbamazepine, Phenytoin, Topiramate, Phenobarbital, Primidone (n=72)	16	5,8	<.001
<i>Valproic acid (n=41)</i>	11	3,3	<.001
Exposed to medication category 2 :			
ACE-inhibitors (n=6)	3	.5	.008
	Anomalies of the respiratory system		
Exposed to medication category 1 :			
Carbimazole, Propylthiouracil, Thiamazole (n=10)	2	.2	.021

We found an –well known from literature- association between the use of antiepileptics and anomalies of the nervous system (16, expected count 5,8, $p < .001$). In more than half of the cases (41 out of 72), valproic acid was used. We therefore also found an association between valproic acid only and anomalies of the nervous system (11, expected count 3,3, $p < .001$).

ACE-inhibitors were also associated with the nervous system anomalies (3, expected count .5, $p = .008$).

In the small group of thyreostatics (carbimazole, propylthiouracil and thiamazole), we found an association with anomalies of the respiratory system (2, expected count .2, $p = .021$). Both cases have lung hypoplasia.

The largest group is formed by the tetracycline antibacterials. We found no statistically significant associations in this group. Apart from the above mentioned associations, we found no significant signals in category 1 and 2 medications.

Only one case was exposed to a medication that nowadays has a PPP. The mother used isotretinoin in the year 2000 and the child suffered from a mild urinary tract anomaly.

New in this report

We found a total of 225 new cases with maternal medication use in 2019. Only five new cases concerned medication with a possible teratogen effect. Within the group of tetracycline antibacterials, we count four new cases with maternal use of these antibiotics. In this medication group, no significant associations with congenital anomalies were found.

Also in the group of thyreostatics, we found one new case. The case doesn't have an anomaly of the respiratory system. The association found within this last group is therefore less significant, compared to the last year report.

Comments

Our yearly check on the use of medications with a possible teratogen effect, results in more or less stable outcome of known cases. After 2000, no more cases exposed to a medication that nowadays has a PPP, were found in our region.